Chapter 1 – General Introduction

Social Information Processing and Its Disorders

Interacting in complex social situations is a skill that the vast majority of human beings take for granted. To successfully engage in social interactions, one needs, at a minimum, to be able to perceive social information, accurately recognise and evaluate such information and, in turn, respond appropriately (e.g., Borod, 1993). Consistent with this general description, Adolphs (2001, 2002) provided a basic framework for conceiving of the broad domain of social information processing as comprising: *social perception, social cognition* and directing *social behaviour. Social perception* refers to the processes for perceiving and recognising social stimuli. *Social cognition* involves higher-order processing, including the evaluation of those social perceptions and the complex integration of that evaluation with one's motivations, emotions, and abilities, to ultimately decide on a social response or action, as well as aspects that might be described as purely cognitive – e.g., 'theory of mind' reasoning (i.e. reasoning about the causal mental states of others, including story vignette characters) and moral reasoning concerning, for example, hypothetical scenarios (e.g., social behaviour; see Adolphs, 2001). Thus, it is suggested that the sub-domains of social perception and social cognition form reciprocal relationships to allow an individual to successfully process and interact within a social world. This thesis will focus more specifically on social perception and those aspects of social cognition that relate more immediately to social perception, in particular, socio-emotional evaluations of social perceptual stimuli.

This thesis begins by focusing on the *social perception* sub-domain of social information processing, in particular, the ability to detect and process emotional cues. Emotional cue processing is of particular relevance to this thesis; and it is reviewed briefly in the following section.

Emotional Processing

As alluded to above, normal social behaviour is predicated, in part, on one's ability to accurately process emotional cues. As such, any deficit in processing of this type will ultimately impact on social behaviour to some degree (Olson, Plotzker, & Ezzyat, 2007). Indeed, it can be

difficult at times to determine whether observed impairments of social cognition and/or abnormal social behaviour reduce to underlying deficits of more basic emotional processing. For example, one's ability to fully understand the mental state of another (i.e., theory of mind) relies on the accurate processing of emotion to develop an appropriate social judgement (Olson, et al., 2007). More recently, however, lesion studies have begun to suggest that explicit emotion cue recognition and higher-order social judgements may be dissociable processes (e.g., Willis, Palermo, Burke, McGrillen, & Miller, 2010). In more detail, Willis and colleagues (2010) found that patients with orbitofrontal (OFC) damage displayed abnormal social judgements, characterised by difficulty using negative facial expressions to guide approachability ratings, despite their explicit emotion recognition abilities remaining intact.

Emotional cue processing is comprised of implicit responses to the emotional cues (i.e., neuropsychophysiological reactions), explicit emotion cue recognition, and, some would argue, emotional memory, which refers to a special category of memory involving the implicit learning and storage of information about the emotional significance of events (Hamann & Canli, 2004; LeDoux, 1993). This latter component of emotional memory is not directly addressed in this thesis, although it is said that emotion cue recognition requires an individual to know something about the world, and therefore requires memory of emotional information of some sort (Adolphs, 2002). The majority of research that has investigated the implicit and explicit emotional processing abilities of typically developing individuals, as well as those with acquired or developmental disorders, has primarily used visual stimuli (i.e., images of emotional faces or social scenes). This is not surprising, firstly, as the visual system is the most well understood sensory system (Graven & Browne, 2008), and secondly because human beings rely heavily on visual non-verbal cues during social interactions (Ekman & Friesen, 2003). A comprehensive review of the literature surrounding the recognition of emotional facial expressions is beyond the scope of this general introduction (although for an excellent review see Adolphs, 2002). The following sections, however, provide a brief overview of facial emotional processing, including

higher-order evaluations of the social significance of facial expressions, in typically developing individuals, as well as in those with acquired and developmental disorders.

Emotional Processing: Typical Development

Research into typically developing individuals suggests that faces represent an exceptional class of stimuli for humans (Farah, Wilson, Drain, & Tanaka, 1998). Newborns are reportedly able to differentiate between the face of their mother and a stranger shortly after birth (Field, Cohen, Garcia, & Greenberg, 1984), and they display preferential behaviour towards face stimuli from as early as a few days old (Morton & Johnson, 1991). Moreover, it has been suggested that children as young as seven months old can discriminate between some basic emotions (Soken & Pick, 1992), which is in line with the evolutionary significance of being able to recognise *emotional* facial expressions. That is, such ability is a fundamental requirement for normal reciprocal social interactions; and allows for an individual to gain socially relevant information about their social counterpart.

The eyes are thought to be particularly important for engaging with others, directing social turn-taking and understanding the more complex mental states of others (see, e.g., Baron-Cohen & Cross, 1992). Not surprisingly then, it is the eyes of emotional facial expressions that typically developing individuals focus on the most. Eye-tracking studies have revealed that typically developing individuals focus primarily on the eyes and then the mouth (e.g., Tanaka & Farah, 1993), which comprise an "upside-down triangle" configuration for holistic or configural processing of a face (Calder & Jansen, 2005; Calder, Young, Keane, & Dean, 2000; Pelphrey et al., 2002).

Explicit emotional processing. With respect to the explicit recognition of emotional facial expressions, researchers have consistently reported that happy faces are recognised more accurately and more quickly than faces portraying any other emotion (e.g., Feyereisen, Malet, & Martin, 1986; Leppänen & Hietanen, 2004; Palermo & Coltheart, 2004). Neutral, angry and surprised facial expressions are reported to be the next most accurately recognised, followed by sad and disgusted expressions (see Palermo & Coltheart, 2004). In contrast, fearful facial

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expressions are reported to be the hardest to recognise, with people being both slower and less accurate when identifying fearful faces (Palermo & Coltheart, 2004; Rapcsak et al., 2000), as well as finding fearful faces more easily confusable with other emotions, such as surprise (Adolphs, 2002).

Implicit emotional processing. Processing emotional facial expressions elicits characteristic physiological and neuronal responses; although these responses are not always distinctive for individual emotions. For example, autonomic nervous system (ANS) activity, such as skin conductance responses (SCRs), cannot be fully differentiated when *viewing* emotional facial expressions; for example, findings from a recent meta-review of 134 articles investigating emotion and ANS arousal revealed that both positive and negative emotional images elicited increased SCRs in typically developing controls to a similar degree (Kreibig, 2010). Interestingly, similar results are seen with regard to SCRs when individuals *express* distinct emotional facial expressions (e.g., happy, sad, fear, anger; Cacioppo, Berntson, Larsen, Poehlmann, & Ito, 1993). As such, SCRs are considered to be sensitive to the general level of arousal associated with the stimulus rather than the particular valence of the stimulus (Critchley, 2002; Lang, Greenwald, Bradley, & Hamm, 1993).

In contrast to the pattern of SCR results, there is good evidence implicating the activation of distinct neural regions when specific emotions are processed. The amygdala is one of the most heavily researched brain regions with respect to emotional processing. Imaging studies with typically developing individuals, complemented by lesion study findings (see below), have consistently shown that the amygdala is involved in the processing of fearful facial expressions (Breiter et al., 1996; Morris et al., 1996; Phillips et al., 1998), even when processing is unconscious (Whalen et al., 1998). The amygdala has also been reported, less consistently however, to be involved in processing other negative emotions such as sadness (Blair, Morris, Frith, Perrett, & Dolan, 1999) and anger (Calder et al., 1996; LeDoux, 1998), but not disgust (Breiter, et al., 1996; Morris, et al., 1996). Rather, the processing of disgusted facial expressions has been associated with the insular cortex and basal ganglia, both in typically developing individuals (Phillips, et al.,

1998; Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998), as well as in patients with Huntington's disease (Jacobs, Shuren, & Heilman, 1995; Sprengelmeyer et al., 1996).

These aforementioned limbic and striatal regions have a multitude of reciprocal connections to other regions, particularly the frontal lobes (Ghashghaei & Barbas, 2002; Ongur & Price, 2000). Not surprisingly then, specific frontal regions have also been associated with socio-emotional processing, and in particular the orbitofrontal cortex (OFC; Hornak, Rolls, & Wade, 1996; Vuilleumier, Armony, Driver, & Dolan, 2001; Willis, et al., 2010). The OFC has been shown to be activated when processing emotional facial expressions in general (Hornak, et al., 1996), and more specifically, the processing of angry facial expressions (Blair, et al., 1999). Moreover, the OFC has been implicated in more higher-order socio-emotional decision making, reviewed below.

Socio-emotional evaluations of emotional faces. The initial holistic visual-scanning of an emotional face, coupled with an appropriate implicit neuropsychophysiological response, may contribute to a more accurate appraisal of another person's mental state, and ultimately may aid the individual to make sound social evaluations of that other person, concerning, for example, whether or not they present any potential threat to the individual. This sort of analysis is supported, to some extent by the literature; for example, when typically developing individuals are asked to rate the approachability of people displaying different emotional facial expressions, they are reported to display a characteristic rank order of ratings. That is, typically developing participants in such a study tend to rate people with happy (i.e., positive) facial expressions as more approachable compared to people with sad and fearful (i.e., non-threatening negative) expressions, with angry (i.e., threatening) expressions being rated as the least approachable (e.g., Porter, Coltheart, & Langdon, 2007; Willis, et al., 2010).

Deficits in the implicit and explicit processing of emotional facial expressions, as well as abnormal social judgements of the approachability of people displaying different facial emotional expressions, have been observed in both acquired and developmental disorders. These include the well-documented cases of patients with specific amygdala or orbitofrontal cortex (OFC) lesions (e.g., Adolphs, Tranel, & Damasio, 1998; Heberlein, Padon, Gillihan, Farah, & Fellows,

2008; Hornak, et al., 1996), as well as individuals with autism, schizophrenia and social anxiety (e.g., Celani, Battacchi, & Arcidiacono, 1999; Edwards, Jackson, & Pattison, 2002; Simonian, Beidel, Turner, Berkes, & Long, 2001), as discussed in more detail below. Exploring emotional processing abilities within these populations allows researchers to better understand socio-emotional development in general, as well as the neural mechanisms that underlie typical socio-emotional development. I begin with a focus on acquired disorders.

Emotional Processing: Acquired Disorders

As mentioned above, individuals with bilateral amygdala lesions are reported to display a selective deficit in recognising negative emotional expressions, particularly fear (e.g., Adolphs, et al., 1998; Adolphs, Tranel, Damasio, & Damasio, 1994; Back, Ropar, & Mitchell, 2007); although not always (see Hamann et al., 1996). Recent studies also suggest that the amygdala may be related to the control of visual scan-paths (Dalton et al., 2005; Marsh & Williams, 2006). More specifically, research suggests that the amygdala primarily responds to the eyes and that paying attention to the eyes is particularly important to detect fearful facial expressions (Whalen et al., 2004). Therefore, amygdala damage may lead to a deficit in appropriately attending to the eyes and a subsequent deficit in interpreting emotional facial expressions, particularly fearful expressions (Adolphs et al., 2005). This impairment in processing facial expressions can lead these amygdala lesion patients to rate negative facial expressions as more trustworthy and approachable than healthy controls (Adolphs, et al., 1998).

Given their impaired emotion recognition abilities, it is therefore somewhat surprising that patients with bilateral amygdala damage can display relatively normal social behaviour (Adolphs, 1999; Anderson & Phelps, 2002). Despite their reported abnormal ratings of trustworthiness from viewing images of emotional facial expressions, these patients are reportedly fully aware of social norms and are able to generate appropriate social reactions from verbal descriptions of social situations (Adolphs, Tranel, Damasio, & Damasio, 1995). These patients also show normal expression of emotion (Anderson & Phelps, 2000) and rate their daily emotional states as similar to the ratings of typically developing individuals (Anderson & Phelps,

2002). According to Phelps and Le Doux (2005), this preserved social behaviour in such patients may relate to intact components of their amygdala functioning (or limbic system functioning, in general), or to cognitive compensation. More specifically, it may be that the understanding of social rules, for example, rules of social turn-taking, and the normal subjective sense of emotional states is sufficient to guide the social behaviour of these patients, particularly if the individual acquired the amygdala damage later in life after a period of typical development (Phelps & LeDoux, 2005).

In contrast to patients with amygdala damage, patients with damage to the OFC are reported to display significant impairments in socio-emotional behaviour and decision making (e.g., see Willis, et al., 2010 for a brief review). However, results from the literature remain equivocal as to whether patients with OFC damage have specific difficulties with explicit emotion recognition. Several studies have shown that patients with OFC lesions have a deficit in recognising emotional facial expressions (Heberlein, et al., 2008; Hornak, et al., 1996). Like the studies of patients with amygdala damage, the majority of these OFC studies have reported that an intact OFC is important in the processing of negative emotions (Iidaka et al., 2001; Ruffman, Henry, Livingstone, & Phillips, 2008), although generalised emotion recognition deficits have also been reported in OFC patients (Heberlein, et al., 2008). In contrast, other lesion studies have reported that patients with OFC damage exhibit intact emotion recognition abilities, despite the presence inappropriate social behaviour in these same patients, as reported either anecdotally by family members (Hornak et al., 2003) or established empirically (Beer, Heerey, Keltner, Scabini, & Knight, 2003; Willis, et al., 2010). These inconsistencies across OFC studies most likely result from differences in the stimuli and methodologies used, as well as individual differences in specific OFC lesion sites and levels of premorbid functioning that can confound lesion studies with small sample sizes.

It is clear from these amygdala and OFC lesion studies, however, that both of these brain regions play important roles in socio-emotional processing; although the roles of each specific brain region are currently not well-defined. While lesion studies are important and provide

invaluable information which, in turn, informs models of typical socio-emotional development, studies of this type also have their limitations. The first, as alluded to above, is that patients with consistent and localized lesions and without more widespread damage are rare. A second limitation is that lesion studies are less useful in informing how socio-emotional processes can develop normally and abnormally from birth. As individuals with acquired disorders develop normally until the time of the acute damage, one cannot assume that the same site of damage will lead to the same consequences in individuals with neurodevelopmental disorders involving analogous regions, who have not experienced this typical developmental trajectory. I consider emotional processing in these individuals in the following section.

Emotional Processing: Neurodevelopmental Disorders

Developmental disorders such as early onset social anxiety/phobia (e.g., Simonian, et al., 2001), autism (e.g., Celani, et al., 1999; Pelphrey, et al., 2002), and schizophrenia (see Edwards, et al., 2002; Marsh & Williams, 2006 for reviews) all have been reported to display emotion recognition deficits. Note that, while the frank psychotic symptoms of schizophrenia do not onset typically until late adolescence, there is some consensus today that schizophrenia is a neurodevelopmental disorder (Bilder, 2001; Lewis & Murray, 1987).

With regard to social anxiety/phobia, Simonian and colleagues (2001) reported that children with social phobia make significantly more errors across emotions when recognising facial expressions compared to well-matched control children. Moreover, both adults (e.g., David & Cutting, 1990; Mandal, Pandey, & Prasad, 1998) and children (e.g., Walker, Marwit, & Emory, 1980) with schizophrenia have also been found to show significant impairments in emotion recognition; with deficits noted more often for negative (e.g., Dougherty, Bartlett, & Izard, 1974) but also positive (e.g., Schneider, Gur, Gur, & Shtasel, 1995) emotions. Additionally, subtle emotion recognition deficits have been noted across the schizophrenia spectrum, including in individuals with Schizotypal Personality Disorder (Mikhailova, Vladimirova, Iznak, Tsusulkovskaya, & Sushko, 1996; Poreh, Whitman, Weber, & Ross, 1994) and first-degree relatives (Bediou et al., 2007).

Interestingly, decreased amygdala activity in response to fearful faces has also been observed in schizophrenia (Schneider et al., 1998; Takahashi et al., 2004; Williams et al., 2004). This amygdala hypoactivation has been linked to abnormal visual scanning of emotional faces, whereby individuals with schizophrenia are consistently found to avoid attending to the internal features of emotional faces – that is, the eyes, nose and mouth (see Marsh & Williams, 2006 for review). This 'restricted' scanning has been observed in both individuals with schizophrenia (Green, Williams, & Davidson, 2003) and their first-degree relatives (Loughland, Williams, & Harris, 2004); and is particularly apparent for negative facial expressions. This abnormal visual scanning of emotional faces has also been found to be associated with difficulties in explicit recognition of facial emotional expressions in individuals with schizophrenia, but not in first-degree relatives (Green, et al., 2003; Loughland, et al., 2004).

Autism is a neurodevelopmental disorder characterised by marked difficulties in social interaction, impaired communication, restricted and repetitive interests and behaviours, and sensory sensitivities (American Psychiatric Association, 2000). Individuals with autism, as well as their first-degree relatives, have also been reported to display emotion recognition deficits (e.g., Bolte & Poustka, 2003; Celani, et al., 1999; Pelphrey, et al., 2002); although not consistently (see Adolphs, Sears, & Piven, 2001). Moreover, those studies which have reported emotion recognition difficulties in individuals with autism have not always shown consistent emotion-specific deficits. For example, Celani and colleagues (1999) reported that, compared to children with Down syndrome (DS; a genetic disorder resulting from a third copy of chromosome 21) and typically developing controls, children with autism were significantly worse at recognising happy and sad expressions. Pelphrey and colleagues (2002) also reported that their sample of males with high-functioning autism displayed overall poorer emotion recognition. However, this deficit was driven primarily by the autistic groups' significantly reduced ability to recognise fearful expressions, and angry expressions to a lesser degree; in line with the pattern of deficits across emotions seen in individuals with amygdala damage (Adolphs, et al., 1998; Adolphs, et al., 1994; Back, et al., 2007).

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Like patients with amygdala damage, individuals with autism are also observed to avoid eye regions when visually scanning emotional faces (Dalton, et al., 2005; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey, et al., 2002). This eye gaze avoidance has been linked to these individuals' difficulty in explicit emotion recognition (Pelphrey, et al., 2002), as well as their abnormal brain functioning (Dalton, et al., 2005). By measuring concurrent visual scan-paths and functional brain activity, Dalton and colleagues revealed that the amount of time spent fixating on the eye region during a facial discrimination task strongly and positively predicted amygdala activation in individuals with autism but not in typically developing controls. They concluded that these amygdala abnormalities in autism might be associated with aberrant emotional face processing (Dalton, et al., 2005)

Findings from these studies investigating individuals across the autism spectrum and across the schizophrenia spectrum suggest a genetic contribution to the development of normal emotional processing skills. This suggestion is consistent with Adolphs' (2001) view that researchers need to consider the role that genetics play in emotion recognition abilities. Indeed, recently, there has been increasing interest in investigating this genotype-phenotype relationship, with a particular focus on using a cross-syndrome approach to compare genetically distinct neurodevelopmental disorders. For example, recent research has focused on comparing the emotional processing abilities of individuals with autism to those with Williams syndrome; a rare genetic disorder characterised by mild-to-moderate intellectual impairment, facial dysmorphology, medical complications and, in contrast to autism, a hyper-social personality (WS; Riby & Hancock, 2008, 2009)[1].

Riby and Hancock (2008) conducted a series of eye-tracking studies to compare the visual face-scanning of individuals with autism and WS. Their findings revealed that, compared to typically developing controls, WS individuals showed prolonged fixations to facial eye regions

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[1] I comment on what is known of the genetics of these two disorders later; for now, I briefly overview some of the more relevant behavioural findings that provide the more immediate backdrop to the research conducted in this thesis.

when these were viewed both within naturalistic social scenes and when images of faces were artificially embedded into unrelated landscape scenes. In contrast, individuals with autism took significantly longer to attend to, and spent significantly less time viewing, facial eye regions compared to their control groups. While Riby and Hancock (2008, 2009) did not directly compare these neurodevelopmental disorders, their findings provided indirect evidence that individuals with WS spend more time attending to salient social information (particularly eyes) than those individuals with autism.

These cross-syndrome findings focused on different neurodevelopmental groups are interesting given the differences in social phenotypes of these two conditions. More specifically, WS is characterised by hypersociability (i.e., indiscriminate approach towards people, including strangers) rather than social avoidance and awkwardness (Mervis, 2003), which is characteristic of autism. However, these previous studies have provided limited insight into the relationship between genes and behaviours. This is because the genetic aetiology of WS has been well identified as involving a deletion on chromosome 7 (Fryssira et al., 1997), whilst there is limited knowledge surrounding the aetiology (genetic or otherwise) of autism. Indeed, current evidence suggests that autism is a highly complex polygene disorder (Abrahams & Geschwind, 2008; Bailey, Phillips, & Rutter, 1996; Sanders et al., 2011). As such, it is difficult to move past the WS and autism phenotypes to better specify the distinct genotypes that may associate with distinct abnormal social phenotypes; and to use this genotypic-phenotypic information to inform models of normal and abnormal social development from birth.

There are, however, other genetically-based neurodevelopmental disorders that also exhibit abnormal social phenotypes that are somewhat similar to the socially avoidant autism phenotype, but for which we know much more about the genetic aetiology. Fragile X syndrome (FXS) is one such disorder, and it is the disorder that I will primarily focus on in this thesis. While an in depth review of the genetic complexities associated with FXS is beyond the scope of this thesis, the following section does provide a brief discussion of the genetic basis of FXS and the resulting heterogeneity seen in the FXS phenotype.

Fragile X Syndrome (FXS)

The FXS Genotype and Phenotype

FXS is a neurodevelopmental disorder that results from large expansions of the cytosine-guanine-guanine (CGG) trinucleotide repeat in the promoter region of the fragile X mental retardation 1 (FMR1) gene (Hatton et al., 2006; Kwon et al., 2001). It affects approximately 1 in 4000 males and 1 in 8000 females (Crawford et al., 1999; Sherman et al., 2002; Turner, Webb, & Robinson, 1996). Typically, normal individuals have between 5 and 40 CGG repeats, and individuals with approximately 45 to 54 are considered to be in a grey zone. Little research has been conducted into this grey zone, however, it has been associated with minor instability between generations (Hagerman, 2006). Individuals with between 55 and 200 repeats are defined as being premutation carriers. While most premutation carriers are considered to have intact intellectual functioning, there is a body of evidence suggesting there is distinct premutation phenotype characterized by similar, but milder, symptoms seen in FXS (see, e.g., Cornish et al., 2005a; Hagerman & Hagerman, 2004; Hessl, et al., 2011).

In individuals with over 200 CGG repeats, the FMR1 gene is silenced and interrupts the production of FMR1 messenger RNA (Verkerk et al., 1991). This interruption in messenger RNA production leads to the failure to produce fragile X mental retardation protein (FMRP; Hagerman, 2002; Tassone et al., 2000). FMRP is believed to be essential for normal brain development and function (Hagerman, 2002; Irwin, Galvez, Weiler, Beckel-Mitchener, & Greenough, 2002; Mazzocco, 2000), playing a particular a role in the maturation of the synapse and pruning of neuronal connections (Hagerman, 2002; Hessl, Rivera, & Reiss, 2004). It is the lack of this protein, and the associated structural and functional abnormalities, that leads to the collection of features that comprise the FXS full mutation phenotype (Irwin, et al., 2002; Mazzocco & Reiss, 1999).

The FXS phenotype can vary greatly across individuals. This is due to the fact that FXS is an X-linked disorders and the amount of FMRP produced depends on several factors including gender and mosaicism. As females have two X-chromosomes, they tend to display a milder phenotype compared to males with FXS. By calculating the ratio of cells that express the

unaffected chromosome versus cells that express the affected chromosome, an activation ratio can be used to estimate FMRP levels, and thus FMR1 gene activation (Mazzocco & Reiss, 1999). Similarly, activation ratios can also be calculated for individuals with mosaicism. Mosaicism refers to a mixed pattern of FMR1 mutation, and refers to both premutation and full mutation alleles (Pieretti et al., 1991) and combinations of full mutation and normal alleles; the latter being the typical genotype of females with the full mutation (Kaufmann et al., 1999). This mixed pattern leads to a variation in FMRP production, and therefore the related phenotype expressed (as discussed below), and helps to explain the heterogeneity observed in both females and male with FXS.

Intellectual impairment is one of the most prominent features of the FXS phenotype (Lewis et al., 2006; Mazzocco, 2000; Mazzocco, Pennington, & Hagerman, 1993; McClennen, 1992; Tamminga & Huber, 2007). In fact, FXS is the most common hereditary cause of intellectual impairment (Feinstein & Reiss, 1998; Mazzocco, Pennington, & Hagerman, 1994); however, individuals with FXS also display behavioural difficulties that are disproportionate to their cognitive impairment (Berry-Kravis & Potanos, 2004). Inattention, impulsivity, and hyperactivity are common, leading to higher than normal rates of Attention Deficit Hyperactivity Disorder (ADHD) diagnoses within the disorder. FXS individuals also show an abnormal social phenotype; for example, these individuals display significant social impairments including: social anxiety, social withdrawal, gaze aversion, hyperarousal, reduced interaction with peers, as well as stereotypic, schizotypal, obsessive-compulsive and autistic social behaviours (e.g., Berry-Kravis & Potanos, 2004; Cohen et al., 1988; Cohen, Sudhalter, Pfadt, Jenkins, & Brown, 1991; Cornish, Munir, & Wilding, 2001; Hagerman, 2002; Hatton et al., 2002; Hessl et al., 2001; Kaufmann et al., 2004). It is these social impairments that are of major interest in this thesis. The following section reviews the relevant literature pertaining to socio-emotional processing within this disorder.

Social Impairments in FXS

Anecdotally, social anxiety is one of the most debilitating asocial symptoms of FXS. It's not surprising then that social anxiety is also one of the most common psychiatric diagnoses reported

in both males and females with FXS (Roberts, Mazzocco, Murphy & Hoehn-Saric, 2008; Roberts, et al., 2007; Tsiouris & Brown, 2004). In addition to social anxiety, both males and females with FXS have also been observed to display other characteristics that impact on their social functioning, such as schizotypal and autistic personality features (Kerby & Dawson, 1994; Tsiouris & Brown, 2004). Schizotypy refers to personality traits such as limited capacity for close interpersonal relationships and eccentric behaviours, as well as odd and unusual perceptions and thinking. Research has shown the females with FXS show significantly higher rates of schizotypal traits compared to familial and intellectually delayed control groups (Sobesky, Hull, & Hagerman, 1994). In fact, Schizotypal Personality Disorder has been found to be the most prominent axis II diagnoses in FXS with 76.9% of FXS females in one study reported to meet DSM-IV criteria for Schizotypal Personality Disorder (Franke et al., 1998). Similar findings have been reported for FXS males (see Kerby & Dawson, 1994).

Features such as echolalia and speech perseverations, hand flapping, delayed imitative and symbolic play, language delay, poor eye contact, and reduced social interaction with unfamiliar people are also commonly reported in FXS individuals (e.g., Fryns, Jacobs, Kleczkowska, & Van den Berghe, 1984; Hagerman & Harris 2008; Kaufmann, et al., 2004). Not surprising then is that approximately 20-30% of individuals with FXS have a comorbid diagnosis of autism (Hagerman, Jackson, Levitas, Rimland, & Braden, 1986; Hatton, et al., 2002; Mineur, Huynh, & Crusio, 2006; Rogers, Wehner, & Hagerman, 2001). However, the prevalence of FXS among individuals with autism is reported to be between 2-5% (e.g., Piven, Gayle, Landa, Wzorek, & Folstein, 1991), suggesting that FXS is not a significant cause of idiopathic autism.

The social anxiety, schizotypal features and autistic tendencies seen in FXS individuals strongly suggest that there may be specific underlying social information processing deficits in this population. The main focus of this thesis is emotional cue processing; and in particular, how individuals with FXS explicitly and implicitly process emotional facial expressions. Previous research investigating emotional processing within FXS is briefly reviewed below.

Explicit Emotional Processing

Early behavioural research into FXS suggested that there is no obvious emotion recognition deficit in either males or females with FXS (Mazzocco, et al., 1994; Simon & Finucane, 1996). Moreover, in those studies that did observe emotion recognition deficits for either basic (happy, sad, fearful, angry) or complex (shame, contempt, interest, surprise) facial expressions in FXS individuals, these deficits were fully accounted for by reduced levels of general intellect (e.g., Turk & Cornish, 1998). However, many of these early behavioural studies employed simple picture-to-picture matching paradigms, where participants were asked to match the target emotion to photographs or schematic drawings of emotional faces. These matching tasks may not be sensitive enough to identify emotion *recognition* difficulties within the FXS population. In more detail, one may be able to successfully complete these picture-to-picture paradigms without knowledge of emotions, rather relying only on perceptual matching (i.e., matching two images based on, for example, similar upward-turned mouths without knowledge that this is indicative of happy facial expressions). Importantly, these tasks may, in fact, not be analogous to the process individuals undertake when assessing the emotional expression of fellow humans in day-to-day life.

The claim that these perceptual-matching tasks may be insensitive in the context of assessing emotional processing in FXS is supported by more recent FXS research which has employed more sensitive tasks that require correct labelling of emotional facial expressions rather than simple picture-matching. Cornish and colleagues (2005a) compared the emotion recognition abilities of FXS male carriers with familial and non-familial age- and gender-matched controls using two tasks: a facial expression recognition test and the Revised Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Results from their study revealed that males with the FXS premutation performed significantly more poorly than both control groups on both tasks; with the deficit most noticeable for neutral facial expressions (Cornish, et al., 2005a). As such,

Papers Two to Four of this thesis partially aim to address this issue of task insensitivity by using labelling tasks to investigate the explicit emotion recognition abilities of FXS individuals.

Consistent with this emerging behavioural evidence of explicit emotion recognition deficits in FXS, albeit in FXS carriers, recent psychophysiological and imaging research has also begun to reveal abnormalities in the implicit processing of emotional information across the FXS spectrum (Dalton, Holsen, Abbeduto, & Davidson, 2008; Farzin, Rivera, & Hessl, 2009; Farzin, Scaggs, Hervey, Berry-Kravis, & Hessl, 2011; Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009; Holsen, Dalton, Johnstone, & Davidson, 2008), as reviewed below.

Implicit Emotional Processing

Physiological findings. With respect to studies of implicit socio-emotional processing, Belser and Sudhalter (1995) were the first to use skin conductance measures to reveal that the two FXS males they studied displayed significantly higher skin conductance levels during conversations, which involved eye contact with a stranger, when compared to males with ADHD or Down syndrome. Farzin and colleagues (2009; 2011) also reported increased pupillary reactivity, which is another index of autonomic nervous system (ANS) activity, in both males and females with FXS compared to chronological age- (CA-) matched controls when the participants passively viewed emotional faces (Farzin, et al., 2009; 2011). Farzin et al. (2009) used eye-tracking to investigate fixations and pupil size responses in a group of 16 adolescent and young adult with FXS as they viewed photographs of calm, happy and fearful facial expression, as well as scrambled faces. Results indicated that, compared to controls, the FXS individuals made fewer fixations to, and spent less time looking at, the eye region of faces. Additionally, the FXS individuals displayed increased pupil reactivity to emotional faces. This increased pupillary response was significantly associated with eye gaze aversion in the FXS group, but not in the CA-matched control group. Interestingly, this pattern was observed in both males and females with FXS, and was not significantly associated with severity of autism symptomology (Farzin, et al., 2009).

Previous FXS research has also indicated that FXS individuals display hyperarousal, not only to social stimuli (Farzin, et al., 2009; 2011; Hall, et al., 2009), but also to non-social stimuli,

such as sensory stimuli (e.g., tactile and auditory stimuli; Hagerman et al., 2002; Miller et al., 1999). Several studies also suggest that FXS hyperarousal can be seen at initial baseline prior to any experimental manipulation involving social stimuli (Hall, et al., 2009; Keysor, Mazzocco, McLeod, & Hoehn-Saric, 2002; Roberts, Boccia, Bailey, Hatton, & Skinner, 2001). More recently, Hall and colleagues (2009) have also reported increased heart rate, not only during a social interaction task, but also at baseline, in their large sample of FXS males and females, when compared to a gender-matched sibling control group. This hyperactivity was observed in addition to, but was not associated with, eye gaze aversion. Findings of this type have led some researchers to suggest that the FXS socio-behavioural phenotype, involving social hyperarousal, is actually secondary to more generalized hyperarousal that then leads to an avoidance of, and/or withdrawal from, social stimuli (Cohen, 1995; Cornish, Sudhalter, & Turk, 2004; Hagerman, 2002). This suggestion is explored in paper four of this thesis.

Next I consider neuroimaging indices that underpin behavioural performances when FXS individuals process emotional cues.

Neuroimaging findings. Dalton and colleagues (2008) simultaneously recording functional imaging and eye-tracking in their study of FXS and autistic individuals processing emotional facial expression during a facial-emotion discrimination task (i.e., participants were asked to judge whether a facial expression was emotional or not). Their results revealed that the FXS individuals displayed a similar, yet less aberrant, pattern of gaze fixations and neural activation, when compared to the individuals with autism. In more detail, the FXS individuals displayed marginally reduced fixations to the eyes and right fusiform gyrus hypoactivation, when compared to controls; a pattern that was also seen in the individuals with autism. The FXS group, however, also displayed significantly greater activation in some other regions including the left hippocampus, left superior temporal gyrus and right insula, when compared to both controls and individuals with autism. Overall, these results suggested a unique underlying neural circuitry in FXS, when processing emotional information, compared to autism (Dalton, et al., 2008).

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Holsen et al. (2008) further investigated these abnormal neural circuits in FXS by correlating brain activation levels during face encoding with levels of social anxiety. Compared to CA-matched controls, the FXS group displayed poorer memory for previously seen fearful faces, significantly fewer eye and face fixations, and a unique pattern of neural activation. More specifically, eye fixations in the FXS group were negatively correlated with activation in the posterior cingular gyrus and insula (believed to be attention and emotion processing regions of the brain) and positively correlated with activation in the angular gyrus (said to be the multisensory processing areas of the brain). Additionally those FXS individuals who self-reported higher levels of social anxiety showed less neural activation in not only frontal regions believed to underpin social cognition, but also the hippocampus, which is the core memory area of the brain, when viewing emotional faces (Holsen, et al., 2008).

These previous psychophysiological and neural findings provide good insight into the neural and autonomic underpinnings of social information processing in FXS, including that: FXS individuals display hyperarousal in social interactions and reduced attention to the eyes of emotional faces, when compared to unaffected siblings (Hall, et al., 2009) and CA-matched controls (Farzin, et al., 2009; Farzin, et al., 2011); as well as distinct neural activation when processing emotional cues and when compared to CA-matched controls as well as to individuals with autism (Dalton, et al., 2008; Holsen, et al., 2008).

There are some limitations of these previous studies that preclude a clear interpretation of their findings. Firstly, none of these previous studies included a mental age- (MA-) matched control group, making it difficult to determine whether the abnormalities seen within the FXS groups were a result of specific deficit or generalised developmental delay. Secondly, the majority of the studies did not also include an explicit measure of emotional processing (e.g., Farzin et al., 2009; 2011), and those that did, used measures that potentially lacked sensitivity (i.e., emotional-discrimination task; Dalton et al., 2008). These concerns about previous studies are generally taken into consideration in the design of the studies in this thesis, which all included both CA-

matched and MA-matched controls, and which concurrently collected implicit and explicit measures of emotional processing (see, e.g. , Papers Two, Three and Four).

Thus far I have reviewed previous studies of emotional cue processing in FXS. The following section focuses on previous FXS studies that have investigated higher-order socio-emotional evaluations.

Socio-emotional Evaluative Judgements

Avoidance during social interactions, including eye gaze aversion, has been well documented in individuals with FXS (Cohen, et al., 1988; Cohen, Vietze, Sudhalter, Jenkins, & Brown, 1989, 1991; Hall, et al., 2009; David Hessl, Glaser, Dryer-Friedman, & Reiss, 2006). Several studies have also empirically investigated aspects of higher-order social cognition within the disorder, with mixed results. For example, studies of emotion attribution abilities, based on a task where participants are asked to judge how someone else would likely feel within different contexts (e.g., how would Mary feel if she got an ice-cream on a hot day?), have reported normal performance in FXS individuals (Turk & Cornish, 1998). However, using two well-standardized tasks of theory of mind (the location change false belief task and the appearance–reality task), it has been reported that children with FXS do display a theory of mind deficit that is comparable to individuals with Down syndrome (Cornish, et al., 2005b). Having said this, Grant and colleagues (2006) reported that the inability of FXS individuals to successfully complete theory of mind tasks, where they must infer that somebody else is acting on a false belief that misrepresents the actual reality, could be explained by executive dysfunction in FXS, specifically, working memory and inhibition deficits (Grant, Apperly, & Oliver, 2006).

To date, no studies have specifically investigated higher-order social cognition judgements that involve the interaction of social-cognitive processing and social processing in FXS individuals. Specifically, no studies to date have empirically and systematically investigated whether FXS individuals make abnormal social evaluations, in particular abnormal social approachability ratings, of strangers depicting certain emotional expressions (e.g., anger). Based on previous findings that FXS individuals show implicit emotional processing abnormalities (e.g.,

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autonomic hyperarousal), in addition to their well-documented social anxiety and autistic tendencies, exploring socio-emotional self-judgements of this type is of particular interest. This will be the aim of Paper Four.

Summary

In sum, as FXS is a single-gene disorder associated with social dysfunction, and with a well-define aetiology, it has the potential to inform the wider literature about how genotype affects social phenotype. To date, however, there has been a surprising lack of research into FXS and its associated social processing difficulties. In particular, there remains a paucity of research which has simultaneously investigated explicit and implicit emotional processing within this disorder. Moreover, as a whole, previous research has neglected to include appropriate CA-matched and MA-matched control groups to elucidate whether observed social abnormalities, whether explicit or implicit, are due to generalised developmental delay or reflect a specific deficit. While early research reported no obvious emotion recognition deficits within FXS (Mazzocco, et al., 1994; Simon & Finucane, 1996), recent evidence, both psychophysiological and neuroimaging, suggests that FXS individuals may indeed display abnormalities in socio-emotional processing, at least implicitly as indexed by psychophysiological measures (Farzin, et al., 2009; 2011; Hall, et al., 2009) and at a neural level (Dalton, et al., 2008; Holsen, et al., 2008). As such, there seems to be a notable gap in the literature between those early behavioural studies of FXS, which reported no emotional processing difficulties, and those more recent neuroimaging studies, which instead, suggest abnormalities. It is the aim of this thesis to start to close this gap in the literature.

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Chapter 2 – Thesis Overview

The four empirical papers that comprise the bulk of this thesis aim to provide a more detailed investigation of the socio-emotional processing abilities of FXS individuals. Specifically, the thesis investigates different aspects of socio-emotional processing at a cognitive, behavioural and psychophysiological level of explanation. The thesis begins by using eye-tracking methodology to compare the underlying attentional mechanisms associated with processing social information in both FXS and WS individuals (Paper One). The remainder of the thesis focuses solely on FXS, with Papers Two and Three investigating the explicit and implicit emotion recognition abilities of FXS individuals, with the later indexed by visual scan-paths and autonomic arousal. The empirical component of the thesis concludes with Paper Four, which explores the higher-order social evaluative judgements of FXS individuals, as related to their emotion recognition abilities by way of examining ratings of approachability of strangers' faces in FXS individuals and CA-matched and MA-matched controls. The final chapter provides a general discussion of the overall findings from this thesis. The specific aims of each paper are outlined in more detail in the following section.

Paper One: Viewing Social Scenes: Comparing FXS and WS

This initial paper employs eye-tracking methodology and a cross-syndrome approach to investigate the role of attention in the visual processing of social information in individuals with FXS compared to those with WS, as well as typically developing CA- and MA-matched controls. There has been detailed research investigating the role of attention in explaining the WS socio-behavioural phenotype (Porter, Shaw, & Marsh, 2010; Riby & Hancock, 2008; 2009a; 2009b Riby, Doherty-Sneddon, & Bruce, 2009; Riby et al., 2011), and in particular attentional disengagement difficulties. While some research has investigated general visual attention in FXS (e.g., Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004, 2007), no previous studies have investigated attention to social information in FXS. Moreover, no previous studies have compared social attention processing using eye-tracking methodology across both FXS and WS.

Specifically, to investigate differences in social attention processing between these disorders, we manipulate the location of social information presented within naturalistic scenes, whilst simultaneously recording visual scan-paths. The specific aim of Paper One is to determine whether one or other or a combination of the attentional mechanisms of: capture, disengagement, and/or general engagement, can explain the disparate socio-behavioural phenotypes observed in FXS and WS.

Paper Two: Emotional Face Scanning in FXS

The focus of the second paper is to investigate how individuals with FXS visually process emotional facial expressions. Eye-tracking methodology is again employed to accomplish this, with the FXS participants' visual scan-paths compared to both CA- and MA-matched controls. In contrast to previous FXS eye-tracking studies (e.g., Dalton, Holsen, Abbeduto, & Davidson, 2008; Farzin, Rivera, & Hessl, 2009; Holsen, Dalton, Johnstone, & Davidson, 2008), happy, angry, fearful as well as neutral facial expressions will be included, and explicit emotion recognition will also be concurrently assessed.

More specifically, Paper Two investigates whether visual social processing abnormalities are apparent in FXS, and if so, whether these can help explain any observed explicit emotion recognition deficits. Several hypotheses are made. Firstly, it is predicted that FXS individuals will display explicit emotion recognition deficits, particularly for negative (angry and fearful) facial expressions, when compared to CA- and MA-matched controls. Secondly, it is predicted that FXS individuals will display abnormal visual scan-paths, when compared to controls, and characterised by avoidance of the eyes, both initially and overall, once again, particularly for negative facial expressions. Thirdly, it explored the relationships between emotion recognition abilities, visual scan-paths, and measures of social anxiety, schizotypy and autism.

Paper Three: Hyperarousal in FXS Females

Paper Three investigates hyperarousal in a sample of FXS females. It has been suggested that individuals with FXS suffer from generalised hyperarousal, which in turn leads to behavioural withdrawal and reduced social interaction (e.g., Belser & Sudhalter, 1995; Farzin, et al., 2009;

Hessl et al., 2002). This study investigates whether the arousal levels of FXS individuals differ, firstly from CA- and MA-matched controls and, secondly, depending on the social relevance and/or emotional valence of the stimuli presented. Skin conductance responses (SCRs) are recorded while FXS participants, as well as CA- and MA-matched controls, passively view two sets of images, one of which is assumed to be more socially salient than the other. That is, one set contains images of faces with direct eye-gaze and the other set contains affectively arousing scenes. The emotion of the stimuli within each stimulus set is also manipulated.

It is predicted that FXS females will display significantly large SCRs compared to both control groups, irrespective of the image sets; that is, they will display generalised hyperarousal. However, it is also predicted that the group differences will be more marked for the direct-gaze emotional faces compared to the affective scenes. Thus, it is anticipated that, while FXS females will display generalised hyperarousal consistent with previous reports (Cohen, 1995; Cornish, Sudhalter, & Turk, 2004), this hyperarousal will be heightened for socially salient information.

Paper Four: Socio-emotional Evaluative Processing in FXS

The final paper focuses primarily on empirically investigating the anecdotally reported reduced social approach behaviours observed in FXS. A secondary aim is to determine whether any abnormalities of social approach ratings can be accounted for by the apparent explicit emotion recognition deficits reported elsewhere in FXS. Thus, Paper Four specifically aims to determine whether individuals with FXS display atypical ratings of social approach, even when any impairment of emotion recognition abilities are taken into account.

Based on previous FXS research into implicit emotional processing (e.g., Dalton, et al., 2008; Holsen, et al., 2008), and findings from Papers Two and Three, it is predicted that FXS individuals will display significant emotion recognition deficits compared to both CA- and MA-matched controls. With respect to their social approach ratings, it is predicted that FXS individuals will rate both positive and negative emotional expressions as less approachable than controls, with these group differences not simply due to this group's poorer emotion recognition abilities. It was further predicted that the typical rank order of approachability (with positive emotional

faces generally rated as more approachable than negative emotional faces by typically developing individuals) would be attenuated in the FXS individuals.

Summary

Overall, this thesis explores socio-emotional processing in FXS. Paper One takes a broad cross-syndrome approach to investigate the basic attentional processes that underpin how individuals with FXS compared to those with WS process visual social information. Papers Two and Three explore the explicit emotion recognition abilities of FXS individuals, while also investigating different aspects of implicit emotion recognition - that is, employing measures of visual scan-paths and autonomic responding. Paper Four focuses on higher-order socio-emotional evaluative processing by investigating, empirically, whether FXS individuals display abnormal social judgements of approachability. The final chapter of this thesis draws together the findings from the four empirical papers and discusses their implications.

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Chapter 3 – Viewing Social Scenes: A Visual Scan-Path Study Comparing Fragile X Syndrome and Williams Syndrome

Viewing Social Scenes: A Visual Scan-Path Study Comparing Fragile X Syndrome and Williams

Syndrome

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Abstract

Fragile X syndrome (FXS) and Williams syndrome (WS) are both genetic disorders which present with similar behavioral problems, but distinct social phenotypes. Despite these social differences both syndromes display poor social relations which may result from abnormal social processing. This study aimed to manipulate the location of socially salient information within scenes to investigate the visual attentional mechanisms of: capture, disengagement, and/or general engagement. Findings revealed that individuals with WS displayed difficulties in disengaging attention away from socially salient information; rather than having their attention more captured by such information. The FXS findings, on the other hand, revealed that individuals with FXS actively avoid social information, at least initially. These findings are discussed in relation to the distinct social phenotypes of these two disorders.

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Viewing Social Scenes: A Visual Scan-Path Study Comparing Fragile X Syndrome and Williams Syndrome

Fragile X syndrome (FXS) and Williams syndrome (WS) are both genetically-defined neurodevelopmental disorders associated with cognitive and intellectual disability. Both syndromes present with cognitive profiles that are characterized by relative strengths in verbal domains along with relative weaknesses on tasks that rely on visuo-spatial skills (Bellugi et al. 1999; Fisch et al. 2007; Freund and Reiss 1991; Mervis et al. 2000; Pennington and Bennetto 1998). They are also both associated with higher than normal rates of attention deficit hyperactivity disorder (ADHD; Leyfer et al. 2006; Porter et al. 2009; Sullivan et al. 2006) and maladaptive behaviors (Fisch et al. 2007; Di Nuovo and Buono 2011), including poor social peer relations (see for example Dykens 2000). Despite these similarities, the social phenotype of these two disorders could not be more distinct. Individuals with FXS are described as socially anxious and withdrawn and tend to avoid eye contact and display reduced interaction with peers (Cornish et al. 2001; Kaufmann et al. 2004; Hagerman, 2002; Hessl et al. 2001; Cohen et al. 1988; Cohen et al. 1991). In accord with these descriptions, the FXS population presents with higher than normal rates of social anxiety, schizotypal personality disorder and autism (Rogers et al. 2001; Franke et al. 1998; Tsiouris and Brown 2004). In stark contrast to FXS, the WS social phenotype is characterized by 'hypersociability' (Jones et al. 2000); that is, individuals with WS present with a social-behavioral phenotype characterized by extremely outgoing behavior (sometimes referred to as social disinhibition), a tendency to pursue interactions with other people whether familiar or unfamiliar, and an unusual heightened attraction to other people's faces and, in particular, a marked increase in direct person to person eye gaze (Mervis et al. 2003; Riby et al. 2009).

While these two social phenotypes appear very different, it has been suggested that similar underlying attentional deficits may contribute to the atypical social behavior seen in each of these disorders (e.g., Cornish et al. 2007; Cornish et al. 2004). Using a cross-syndrome approach to directly compare social perception and attention in FXS and WS, the current study explored how attentional abnormalities may help to explain these unusual, yet distinct, social phenotypes.

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Additionally, we compared these two clinical groups to both a chronological age (CA-) and mental age (MA-) matched control groups; which is one of the most commonly used and rigorous methodological approaches for investigating behavioral deficits in individuals with developmental disorders (e.g., Scerif et al. 2004; also see Thomas et al. 2009 for a brief review). More specifically, we use eye-tracking methodology, which provides a direct means of examining the attentional and cognitive strategies used to process a visual scene. Visual scan-paths reveal, in real-time, the way sensory stimuli are processed by representing the spatio-temporal location of directed attention (Noton and Stark 1971). As Duchowski (2007) asserted, measuring real-time attention may give us a better insight into what the observer found interesting; that is, what drew their attention and how that individual perceived the scene. As we were interested in social perception, we recorded visual scan-paths while participants viewed social scenes involving one or more people to investigate attention to the social information within each scene. Firstly, the attentional profiles of these two disorders are discussed.

Attention in Fragile X Syndrome and Williams Syndrome

Inattention, hyperactivity and impulsivity are commonly reported as core behavioral features of both males and females with FXS (e.g., Baumgardner et al. 1995; Lachiewicz and Dawson 1994; Turk 1998), as well as those with WS (Elison et al. 2010; Einfeld et al. 1997). It is not surprising then, as mentioned above, that the prevalence rate of ADHD is significantly higher in FXS and WS compared to the general population. Based on DSM criteria, prevalence rates of ADHD have been reported to range from 41% to 93% in FXS (see Sullivan et al. 2006 for a comprehensive review) and 20% to 65% in WS (Porter et al. 2009; Leyfer et al. 2006).

Consistent with the behavioral reports of ADHD in FXS and WS, specific higher-order attentional deficits have been consistently reported in both syndromes. For example, both children (Munir et al. 2000; Wilding et al. 2002) and adults (Cornish et al. 2001) with FXS have been reported to display impairments in attentional flexibility. Moreover, both toddlers and children with FXS also demonstrate deficits in planning and organizing visual searches as well as inhibiting task-irrelevant responses (Munir et al. 2000; Scerif et al. 2005; 2007). Individuals with

WS are also reported to display deficits in attentional flexibility, typically in the form of an attentional disengagement impairment (i.e., taking longer to disengage from one stimulus to attend to another). Attentional disengagement problems have been reported across the WS lifespan, and for a large number of different stimuli including: non-social stimuli such as diamond shape cues (e.g., Brown et al. 2003; Cornish et al. 2007; Lense et al. 2011; Lincoln et al. 2002) as well as social stimuli such as faces (e.g., Mervis et al. 2003; Riby and Hancock 2009a). Together, these findings suggest that higher-order attentional deficits are apparent in both FXS and WS from an early age.

With the seemingly similar attentional control difficulties observed in both FXS and WS, several studies have directly compared attentional skills across these two disorders (Scerif et al. 2004; Cornish et al. 2007). Using a visual search task, Scerif and colleagues (2004) found that while the FXS and WS toddlers displayed similar performance in terms of search speed and search path compared to CA- and MA-matched controls, both clinical groups made significantly more errors, with the types of errors differing between the clinical groups. In more detail, toddlers with FXS produced more repetitive errors, suggestive of significant behavioral disinhibition; which is consistent with findings from older FXS children (Wilding et al. 2002). In contrast, toddlers with WS made significantly more distraction errors, suggesting a difficulty with visuo-perceptual discrimination (Scerif et al. 2004). Cornish and colleagues (2007) used eye-tracking to further explore differences in directing and inhibiting attention in toddlers with FXS and WS and MA-matched typically developing controls. Consistent with previous findings, the pattern of results suggested that the FXS toddlers displayed significant disinhibition (see Scerif et al. 2005; Wilding et al. 2002; Scerif et al. 2004). On the other hand, the WS toddlers displayed an inability to disengage attention from the initial fixation point, and the WS toddlers were also significantly slower to attend on the incongruent trials of the directing attention task (Cornish et al. 2007). Together, these results provided evidence of problems disengaging away from an attended location in WS; consistent with previous WS research (e.g., see Brown et al. 2003).

In sum, both FXS and WS are associated with attentional control difficulties. Moreover, both FXS (Cornish et al. 2007; Cornish et al. 2004) and WS (Riby et al. 2009; Riby and Hancock 2008; Riby and Hancock 2009) researchers have asserted that these general attentional control difficulties may underlie, at least in part, the atypical social behavior observed in the two disorders; much in the same way that attention modulates social interactions for typically developing individuals (see Fox 2005 for a detailed review). To date, investigations into the general attentional mechanisms that may underlie aberrant social behavior have begun with respect to WS (Mervis et al. 2003; Riby et al. 2009; 2011; Riby and Hancock 2008; 2009a,b), but no studies have explored whether general attentional difficulties of this type may help to explain the FXS social phenotype. The following section moves to consider social attention processing in FXS and WS.

Attentional (Dis) Engagement and Capture: Processing Social Information

WS researchers have used eye-tracking technology to link general difficulties with attentional disengagement to abnormal processing of emotional faces, when such stimuli are viewed in isolation (Porter et al. 2010; Riby et al. 2009). For example, a pattern of atypical prolonged attention to the eye region in WS was first reported by Riby and colleagues (2008; 2009) and later by Porter et al. (2010). In more detail, Porter et al. (2010) found that, once the WS individuals attended to the eye region of a face, they spent significantly more time looking at this region. This was despite the fact that the eye region of a face did not appear to capture the attention of WS individuals any faster than MA-matched controls. These results supported previous observations and anecdotal reports that individuals with WS display an unusual attraction to people's faces and, in particular, their eyes (Riby et al. 2009; Mervis et al. 2003). These results are also consistent with previous studies of WS which show general difficulties with attentional disengagement when processing non-social stimuli (e.g., Cornish et al. 2007; Lincoln et al. 2002). However, more recently, Riby and colleagues (2011) extended their work to more directly tease apart four different components of attentional processing of faces in WS. Results revealed that WS individuals and typically developing controls were equivalent in terms of

performance on tasks of attentional capture by faces, face interference and face bias, but WS individuals displayed significantly larger attentional disengagement effects. That is, the difference in time taken to disengage from faces, compared to objects, was significantly larger for WS than typically developing controls.

With respect to FXS, a limited number of eye-tracking studies have investigated face processing in FXS. These studies have reported that individuals with FXS show fewer fixations to, and spend less time looking at, the eye region of faces compared to CA-matched controls (Dalton et al. 2008; Farzin et al. 2009; 2011; Holsen et al. 2008; Shaw & Porter, 2012), but not MA-matched controls (Shaw and Porter, 2012). FXS individuals have also been reported to display a similarly aberrant, yet less extreme, pattern of gaze fixations when compared to individuals with autism (Dalton et al. 2008). None of these FXS studies, however, have linked face processing to underlying attentional processes.

Using isolated faces, without providing a context, is also considered to be less informative (Birmingham et al. 2008), with researchers arguing that photographic or movie images of people engaged in social context are a more ecologically valid way to study how different populations process social information (Smilek et al. 2006; Riby and Hancock 2008). The use of such stimuli with eye-tracking paradigms is beginning to emerge in research into neurodevelopmental disorders, such as autism (Klin et al. 2002), as well as more recently with WS (Riby et al. 2009; Riby and Hancock 2008; 2009a,b). However, to date, there are no published eye-tracking studies investigating how individuals with FXS process naturalistic social scenes.

In contrast to this lack of eye-tracking research investigating how FXS individuals process information within social contexts, Riby and colleagues have investigated how WS individuals process social scenes in some detail. Consistent with behavioral reports of prolonged attention to faces in WS (e.g., Mervis et al. 2003), Riby and Hancock (2008) found that compared to both controls and individuals with autism, individuals with WS showed prolonged fixations to facial eye regions, but not the mouth regions of faces, when these were viewed within photographic social scenes. Riby and Hancock (2009a) also investigated whether faces that had been artificially

embedded into unrelated landscape scenes captured the attention of children and adults with WS compared to MA-matched controls and individuals with autism. Contrary to their prediction, the WS group did not differ from controls in the time taken to detect and make their first fixation to the face. However, once attention had shifted to the face, the WS group displayed prolonged fixations to the face compared to controls. These finding were replicated and generalized to dynamic (i.e., movie) stimuli (Riby and Hancock, 2009b).

Thus, researchers (Porter et al. 2010; Riby and Hancock 2008; 2009a,b; Riby et al. 2011) have provided consistent support for attentional disengagement difficulties in WS for faces both in isolation and within social scenes, but no clear support for abnormal attentional face capture. Others have, however, reported evidence for abnormal attentional capture for socially relevant information in WS (Tager-Flusberg et al. 2007). In more detail, Tager-Flusberg et al. (2007) employed a change detection task and found that individuals with WS reported significantly more person-related changes when viewing dynamic social scenes (i.e., better change detection for socially relevant information) compared to intellectually impaired controls; suggesting an abnormal attentional bias to visual social information in WS. As Riby and colleagues (2011) concede, these disparate results may relate to the stimuli and tasks used. Tager-Flusberg and colleagues (2007) used whole individuals embedded within dynamic natural scenes compared to grey-scale faces, either in isolation (Porter et al. 2010; Riby et al. 2011) or embedded artificially within scenes (Riby and Hancock 2009a). Moreover, Riby and Hancock's (2009a) embedded-face experiment is the only study to date that has manipulated the location of the social information within the scenes. In more detail, the presentation of socially relevant information at the initial point of fixation in previous experiments (Porter et al. 2010; Riby and Hancock 2008) may have confounded the design with regard to revealing possible evidence of attention capture by such information. That is, as the social information was presented at the point of first fixation, no capture of attention from elsewhere is required or can be measured.

With respect to FXS, while anecdotally it has been reported that individuals with FXS avoid attending to faces (e.g., Cohen et al. 1988; 1991), empirical studies of attentional capture

by, and disengagement from, faces and people are surprisingly lacking in the FXS literature. Research of this type on individuals with idiopathic autism does, however, suggest that these individuals fail to display the typical enhanced attentional capture by faces over objects (Klin et al. 2002). Individuals with idiopathic autism also take significantly longer to attend to faces, and spend less time viewing faces, compared to CA- and NV-matched controls (Riby and Hancock 2008; 2009). Due to the high level of autistic features in FXS, it is plausible, therefore, that FXS individuals may display a similarly reduced level of attentional engagement with social information as those individuals with idiopathic autism. That is, they may display reduced attentional capture by social information, or a general lack of interest in social stimuli, or they may even actively avoid social stimuli due to their well-documented social aversion (e.g., Cohen et al. 1988; Cornish et al. 2001).

Moreover, importantly, no research to date has directly compared visual scanning of social scenes in individuals with FXS and WS. Direct comparison of this type may provide more detailed information about the underpinnings of both aberrant and typical social processing, particularly with respect to the attentional mechanisms of capture, engagement and disengagement in relation to social information processing in FXS and WS.

Study Aims

The overall aim of the current visual scan-path study was to manipulate the location of socially salient information, in particular people's faces and bodies, within natural social scenes to investigate whether one or other or a combination of the attentional mechanisms of: capture, disengagement, and/or general engagement can explain the FXS and WS social phenotypes. To accomplish this, we recorded eye-scan paths whilst FXS and WS individuals and both CA- and MA-matched control participants passively viewed social scenes and we manipulated the location of the main social information within the scenes to be presented either directly at the site of initial fixation (*centrally located*) or away from the initial site of fixation (*non-centrally located*). We investigated three different hypotheses, as outlined below.

Hypothesis 1: Attentional Capture by Social Information

If individuals with WS are more attracted to socially salient information than controls, as suggested by Tager-Flusberg et al. (2007), and as originally hypothesized by Riby and Hancock (2009a), then one would expect the WS group to be significantly faster to shift attention away from initial central fixation to attend to social information that appears elsewhere in the social scene (what we refer to as *non-centrally located* social stimuli). That is, it is hypothesized that the social information that is not immediately available will capture the attention of WS individuals faster than FXS individuals or MA- or CA-matched controls. In contrast, and as based on the autism literature, there is no reason to expect similar attentional capture by social information that is not directly available in FXS individuals compared to MA- and CA-matched controls. Thus there will be no differences in the time taken to shift attention away from initial central fixation to attend to social information that appears elsewhere across the FXS group and the MA- and CA-matched controls.

In sum, if the social attentional capture hypothesis accurately describes the social phenotype of WS, but not FXS, there will be a dissociation between the groups with regard to the time taken to initially move from fixation to fixate on the *non-centrally located* social information in natural visual scenes.

Hypothesis 2: Attentional Disengagement from Social Information

On the other hand, if individuals with WS have greater difficulties with disengaging attention away from social information, as reported by both Riby and Hancock (2009a, b) and Porter et al. (2010), then the WS group is expected to take longer to shift their attention away from social information presented immediately near fixation. Therefore, we predict that it will take longer for the WS group to make their first saccade away from *centrally located* social stimuli relative to the FXS group as well as the CA- and MA-matched control groups. This would be due to these WS individuals' inability to disengage their attention away from the immediately presented socially salient information. In contrast, while individuals with FXS also have problems switching attention, they are also reported to display significant avoidance of social information. Based on

this aversion to social stimuli, one might predict that the FXS individuals in the current study would display no difficulties disengaging attention away from social information presented immediately near fixation. Indeed, we predict that the FXS individuals may, in fact, make initial saccades away from the centrally presented social information faster than compared to the WS individuals or MA- or CA-matched controls. This latter finding would be more consistent with the view that individuals with FXS actively avoid social information.

Therefore, if the attentional disengagement hypothesis can explain the social phenotype of both WS and FXS, we would predict a dissociation between these two clinical groups with WS individuals being slower, and FXS individuals being faster, at saccading their attention away from *centrally located* social information within social scenes.

Hypothesis 3: Attentional Engagement with Social Information

Alternatively, the WS and FXS social phenotypes may be best explained by the level of general engagement the groups display towards social information. As mentioned above, WS individuals typically display a heightened attraction to social information, particularly faces (e.g., Mervis et al. 2003). As such, based on this previous research, if the WS social phenotype can be explained simply by a general interest in social information, we would predict that our WS individuals will spend significantly more time overall attending to the social information within a scene compared to FXS individuals or MA- or CA-matched controls. In contrast, based on the known social avoidance observed in FXS, if a general disinterest in, or potential avoidance of, social stimuli could explain the FXS social phenotype, we would predict that our FXS individuals will spend significantly less time overall attending to the social information within the naturalistic scenes when compared to WS individuals or MA- or CA-matched controls.

That is, if the WS and FXS social phenotypes can be explained by the level of general interest in, or in the FXS case disinterest/avoidance of, social information we would predict that the WS individuals would spend significantly more time overall, and the FXS individuals significantly less time overall, attending to the social information within a naturalistic scene when compared to each other and the control groups.

Method

Participants

Participants were 14 individuals with FXS, 14 individuals with WS, 28 typically developing CA-matched controls and 28 typically developing MA-matched controls[1]. All participants displayed normal or corrected to normal vision. Table 1 displays the mean CA, MA and FSIQ for each group. Appendix 1 includes a table containing demographical details of each clinical participant individually.

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 (2 male; 12 female). CA ranged from 12.08 to 51.42 years (M = 23.01 years, SD = 10.49). MA was established using the Wechsler Abbreviated Intelligence Scale (WASI; Psychological Corporation. (1999). Wechsler Abbreviated Scale of Intelligence (WASI) manual 1999). MA ranged from 6.05 to 21.08 years (M = 8.67 years, SD = 3.93). All FXS participants exhibited the clinical phenotype associated with FXS and genetic testing confirmed the characteristic >200 CGG repeats associated with the disorder (11 Southern Blot, 3 Cytogenic). FXS participants were screened for a history of neurological and psychiatric compromise that was not a part of their FXS profile. On this basis, no FXS participants were excluded. In terms of autistic features, one individual with FXS met the ABC cut-off indicative of autism.

Williams syndrome (WS) participants. WS participants were recruited through the Williams Syndrome Association of Australia (9 male; 5 female). CA ranged from 11.42 to 37.42 years (M = 22.18 years, SD = 8.68). MA was established using the Woodcock-Johnson Test of Cognitive Ability-Revised (Woodcock and Mather 1989). MA ranged from 5.75 to 10.75 years (M =

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[1] Separate CA- and MA-matched control groups were initially recruited for the FXS and WS groups due to sporadic recruitment of clinical participants. Fourteen controls were individually matched to FXS participants on sex and CA (M = 23.81 years, SD = 12.44, p = 0.856), and 14 matched on sex and MA (M = 9.51 years, SD = 3.64, p = 0.564). Likewise, 14 controls were individually matched to WS participants on sex and CA (M = 22.53 years, SD = 8.66, p = 0.916), 14 on sex and MA (M = 7.84 years, SD = 1.66, p = 0.924). Ultimately, the FXS and WS groups were well matched on both CA and MA, so separate control groups were not required. As such, controls were combined to increase power and to allow for a direct comparison across the four groups.

7.71 years, SD = 1.73). All WS participants exhibited the medical and clinical phenotype associated with WS and genetic testing (FISH test) confirmed the characteristic WS deletion (absence of one copy of the Elastin gene on chromosome 7; Fryssira et al. 1997). Consistent with the FXS participant, all WS participants were free from other neurological and psychiatric disorders not considered part of the typical WS profile, and none met cut-off of autism on the ABC.

Typically developing control participants. Typically developing control participants were recruited through the Macquarie University Kids' Science Club and via advertisements distributed across the Macquarie University campus. For both control groups, MA was confirmed using the WASI (Psychological Corporation 1999). Exclusion criteria were a history of learning difficulties, developmental delay, intellectual impairment, as well as behavioral, psychological, sensory or cognitive deficits or a history of neurological compromise. No controls were excluded on these grounds, and none were close to the cut-off on the ABC for autism.

Table 1

Mean (standard deviation) CA, MA and FSIQ by group

	FXS Group	WS Group	MA-matched Group	CA-matched Group
	Mean *(SD)* Range	Mean *(SD)* Range	Mean *(SD)* Range	Mean *(SD)* Range
N	14	14	14	14
% females	87.5%	35.7%	60.7%	60.7%
CA [a]	23.0 *(10.5)* 12.1-51.4	22.2 *(8.7)* 11.4-37.4	8.7 *(3.9)* 5.5-20.4**	23.2 *(10.5)* 11.3-53.1
MA [a]	8.7 *(3.9)* 6.1-21.1	7.9 *(1.6)* 6.2-11.1	8.7 *(2.9)* 5.8-20.4	23.2 *(10.5)* 11.3-53.1**
FSIQ [b]	64 *(14.7)* 52-96	56 *(13.1)* 41-81	107 *(9.1)* 93-126**	106 *(9.0)* 91-128**

[a] Mean CA and MA in years
[b] FSIQ = Standard Score (mean = 100, SD = 15)
Significant difference between clinical groups and relative control group at: * = $p \leq 0.05$; ** = $p \leq 0.01$

As displayed in Table 1, an independent sample t-test revealed that there was no significant difference between the FXS and WS groups on FSIQ [$t(26)$ = 1.48, p = 0.148]. One-way ANOVAs also indicated that the control groups were well matched to the clinical groups, with no significant difference in CA between the FXS, WS and CA-matched control groups [F (2, 53) = 0.05, p = 0.955] and no significant difference in MA between the FXS, WS and MA-matched control groups [F (2, 53) = 0.36, p = 0.699]. There was also no significant difference in sex distribution across the groups, although a trend was observed [χ^2 (3, N = 84) = 7.34, p = 0.062].

Materials

Stimuli included 18 images of social scenes (i.e. scenes involving one or more people) taken from the International Affective Picture System[2] (IAPS; Lang et al. 1999). The IAPS is a set of photographs based on a dimensional model of emotion and contains various pictures depicting animals, social scenes and landscape scenes, among others. The IAPS is widely used in studies of emotion and has been characterized primarily along the dimensions of valence, arousal and dominance (see Mikels et al. 2005 for a review). Each image chosen for the current study contained at least one person in a natural scene. Scenes were presented at a standard size of 25.14 cm (950 pixels) wide by 18.84 cm (712 pixels) high, appearing in the center of the computer screen.

The images were divided into two sets: (1) *centrally located* social stimuli where the socially salient information, in particular involving another person's face, was presented near central fixation point and (2) *non-centrally located* social stimuli where the social aspects of the scene, in particular a person's face, was presented away from the initial central fixation point (see procedure below for more detail). More specifically, a scene was deemed *centrally located* social stimuli if a person's face or body fell within 1° of visual angle from the center of the image (equivalent to the size and location of the initial fixation point). Those scenes in which no part of a person fell within this range were deemed *non-centrally located* social stimuli. There were nine

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[2] Images used in the current study included: central: 2396, 2398, 2480, 2560, 2593, 2745, 2749, 5875, 9913; non-central: 2272, 2299, 2393, 2575, 2579, 2590, 2594, 2598, 7550.

images in each set, matched on valence (*centrally located*: M = 5.56, *SD* = 0.96; *non-centrally located*: M = 5.49, *SD* = 1.26; p = 0.854) and arousal (*centrally located*: M = 3.60, *SD* = 0.63; *non-centrally located*: M = 3.79, *SD* = 0.35; p = 0.569).

Procedure

Participants were seated in a darkened room in a comfortable chair and viewed the images on a Dell 16" CRT monitor from a distance of 60 cm (viewing distance controlled by seat position). The horizontal visual angle was 22.73° and a vertical visual angle was 17.43°. The 18 images were displayed in a pseudo-randomized order for all participants. The experiment lasted approximately 10 minutes including initial equipment set-up and calibration procedure.

Visual scan-path recording. Eye movements were recorded with the Eyelink-II gaze monitoring system (SR Research Ltd.), sampling at a temporal resolution of 500 Hz and with a spatial resolution of 0.2°. An eye movement was classified as a saccade when its distance exceeded 0.2° and velocity reached 30°/s, or when its length exceeded 0.2° and its acceleration had reached 8000°/s^2.

The head-mounted apparatus used to record eye-movements was adjusted to obtain binocular eye movements. Prior to the experiment a nine-point calibration of eye fixation position relative to the screen was conducted. Participants viewed a centrally placed black dot (10mm in diameter) with a white center (2mm in diameter) which moved to eight locations around the periphery and center of the screen. Participants were asked to fixate on the central dot and track its movements with their eyes. The dot moved to a new location once the computer had recorded an adequate corneal 'lock' from the participant, requiring at least 1,000ms viewing in each position of the dot. A successful calibration meant that a robust fixation recording could be obtained across the entire width and breadth of the computer screen. The experimental procedure only proceeded once a satisfactory calibration was achieved. The initial point of retinal attention was controlled by a black dot presented centrally for 1,000ms immediately prior to each face stimulus.

Participants passively viewed the social scenes as they were presented in a pseudo-random order for 10,000ms each. Before each image would appear on screen participants were required to fixate for 2,000ms on the central fixation dot, which then disappeared and was replaced by a social scene. This procedure ensured that all participants were attending to the center of the screen when the image appeared. After 10,000ms the image disappeared and was again replaced by the fixation dot. Manual experimenter control initiated the next trial. While some previous studies have used a shorter display time (e.g., 2,000ms or 5,000ms), we used 10,000ms because we wanted to ensure sufficient time to test for both attentional capture and attentional disengagement. Using a shorter viewing time, we might not have found the patterns of behavior we were interested in.

Defining areas of interest (AOIs). Regions of interest were drawn for each social scene using the 'freehand' drawing function provided in the EyeLink DataViewer. For each scene, a 'social' area of interest (AOI) was designated; defined as the sum of all body parts within the scene.

Visual scan-path parameters. Visual scan-path parameters included: Mean Time to First Fixation on a defined area of interest; Mean Time of First Saccade defined as the mean start time of the first saccade out of an area of interest; and Mean Dwell Time Percent defined as the mean percentage of time spent attending to an area of interest relative to total time spent attending to the computer screen. A Proportional Mean Dwell Time Percent was also calculated for an area of interest (calculated as the Mean Dwell Time Percent to an area of interest divided by the Mean Dwell Time Percent to the whole image of the scene).

Mean Time to First Fixation for an indirect social area of interest was the variable used to test Hypothesis 1 concerning attentional capture by *non-centrally located* social information. Mean Time of First Saccade from a direct social area of interest was used to test Hypothesis 2 concerning attentional disengagement from *centrally located* social information. Proportional Mean Dwell Time Percent was used for all analyses investigating Hypothesis 3 concerning general interest in social information.

Results

Given the small sample size of the current study, a *p* value of 0.05 was used to indicate significance in order to minimize the possibility of Type II error (see Rothman 1990). To correct for violations of the normality and heterogeneity of variance assumptions, respectively, log transformations were conducted on the variables: Mean Time to First Fixation to the *non-centrally located* social areas of interest and Mean Time of First Saccade away from the *centrally located* social areas of interest. Group means (and standard deviations) for all relevant visual scan-path parameters can be found in Table 2.

Table 2

Mean (standard deviation) for each visual scan-path parameter by group (raw data)

	MTFF (non-central social)	MTFS (central social)	pMDTP (central social)	pMDTP (non-central social)
FXS Group	1257.5 *(927.3)*	820.4 *(259.8)* [b]	34.9 *(9.9)*	35.2 *(9.9)*
WS Group	1479.9 *(1013.2)*	1449.4 *(832.3)*	46.9 *(12.1)* [c]	31.9 *(10.4)* [d]
MA Group	1472.0 *(1256.2)*	1308.3 *(449.8)*	39.4 *(8.7)*	34.6 *(10.1)*
CA Group	769.0 *(673.7)* [a]	1148.3 *(533.8)*	40.1 *(10.3)*	38.9 *(8.3)*
	1203.2 *(1028.5)*	**1197.2 *(563.1)***	**40.1 *(10.5)***	**35.7 *(9.7)***

MTFF = Mean Time to First Fixation to non-centrally located social information (ms)
MTFS = Mean Time to First Saccade away from centrally located social information (ms)
pMDTP = Proportional Mean Dwell Time Percent to centrally and non-centrally located social information (%)
Significant group differences between: [a] CA-matched and all other groups (*ps* ≤ 0.049); [b] FXS and all other groups (*ps* ≤ 0.025); [c] WS and all other groups (*ps* ≤ 0.043); and [d] WS and CA-matched controls (*p* = 0.027)

Hypothesis 1: Attentional Capture

To determine whether our WS group was significantly more attracted to social information, we focused solely on the set of *non-centrally located* social stimuli and used Mean Time to First Fixation to the *non-centrally located* social area of interest as the dependent variable (DV). A one-way analysis of variance (ANOVA) with Group (WS, FXS, MA-matched, CA-matched) as the between groups factor indicated that there was a significant difference between the four

groups [F (3, 80) = 4.45 p = 0.006, n^2 = 0.143]. Figure 1a displays the Mean Time to First Fixation to the *non-centrally located* social area of interest for each group.

As seen in Figure 1a, follow-up analyses revealed that the CA-matched control group showed significantly faster initial fixations towards social information presented away from the fixation dot compared to the WS (p = 0.005, d = 0.79), FXS (p = 0.049, d = 0.68) and MA-matched (p = 0.002, d = 0.88) groups. In fact, Figure 1a shows that, contrary to our attentional capture hypothesis, the WS group took more time, rather than less time, albeit not significantly, than even the FXS group to shift attention away from central fixation to initially attend to the social information within a *non-centrally located* social scene.

Based on these results there was no indication of social attentional capture for either clinical group or the MA-matched control group. Rather, only the CA-matched controls displayed any evidence of relative attentional capture by *non-centrally located* social information when compared to the other groups.

Hypothesis 2: Attentional Disengagement

To determine whether our WS group were slower and our FXS group were faster at disengaging their attention away from immediately available social information we focused only on the *centrally located* social stimuli set and used Mean Time of First Saccade away from the *centrally located* social area of interest as the DV. A one-way ANOVA with Group (WS, FXS, MA-matched, CA-matched) as the between groups factor revealed a significant difference between the four groups [F (3, 80) = 4.27, p = 0.008, n^2 = 0.138].

As seen in Figure 1b, follow-up analyses revealed that the significant difference was driven primarily by the FXS group. Specifically, the FXS group was significantly faster at disengaging their attention away from the *centrally located* social stimuli compared to the WS group (p = 0.003, d = 1.06), as well as the MA-matched (p = 0.025, d = 0.82) and CA-matched (p = 0.002, d = 1.26) control groups. It is worth noting, however, that the general pattern of results was such that the WS showed the longest Mean Time to First Fixation away from the *centrally located* social area of interest, compared to all other groups, although, only significantly so

compared to the FXS group. These results provide evidence for active social avoidance within our FXS group, but no real support for the presence of social disengagement difficulties within our WS group[3].

Hypothesis 3: General Attentional Engagement

To examine the general salience of social information across groups, we focused on the Proportional Mean Dwell Time Percent for the social area of interest within a scene as our DV. A mixed ANOVA with Stimulus Set (*centrally located* social stimuli, non-*centrally located* social stimuli) as the within-groups factor and Group (FXS, WS, CA-matched, MA-matched) as the between-groups factor revealed no significant main effect of Group [F (3, 80) = 1.31, p = 0.279, n^2 = 0.05]. However a significant main effect of Stimulus Set [F (1, 80) = 14.11, p < 0.001, n^2 = 0.15], and a significant Group by Stimulus Set interaction [F (3, 80) = 5.12, p = 0.003, n^2 = 0.16] were observed.

The significant Group by Stimulus Set interaction is displayed in Figure 1c and suggests that the WS group spent more time attending to social area of interest in the *centrally located* social stimuli compared to all other groups. Consistent with Figure 1c, follow-up analyses indeed indicated that the WS group spent significantly more time attending to social information that was presented centrally compared to the FXS (p = 0.002, d = 1.25), MA-matched control (p = 0.026, d = 0.77) and CA-matched control (p = 0.043, d = 0.63) groups. Interestingly, the WS group spent significantly less time attending to the social area of interest for the *non-centrally located* social stimuli compared to the CA-matched controls (p = 0.027, d = 0.79). No other significant differences were observed between the FXS, MA- and CA-matched control groups (*ps* ranged from 0.099 to 0.856). These results suggest that in contrast to our prediction, the FXS group overall spent a similar amount of time as the MA- and CA-matched controls attending to social

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[3] With the exception of observed reductions in the significance values of the planned comparison, the pattern of results remained the same when the two FXS males were excluded from the analyses. Box-plots revealed that these FXS males were not outliers on any of the visual scan-path parameters of interest, nor was there any significant correlation between IQ and any of the variables of interest. As such, the reductions in significant levels most likely represent a lack power due to the decreased sample size. These male participants were therefore retained in the analyses.

information. However, interestingly, WS individuals in general spend more time attending to social information which is immediately available, but less time attending to social information
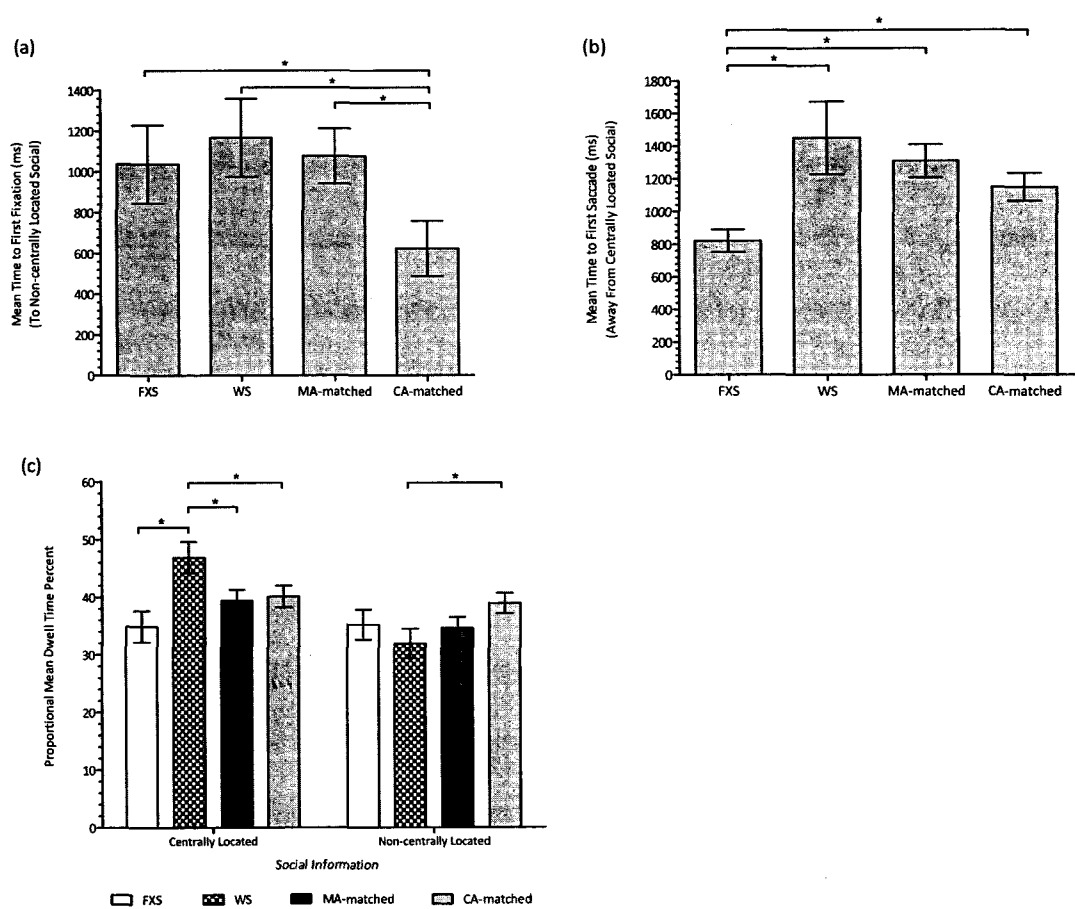
which is in the periphery.

Figure 1. (a) Mean Time to First Fixation (and standard error) to the *non-centrally located* social area of interest within the *non-centrally located* social stimuli. Raw data displayed. (b) Mean Time to First Saccade (and standard error) away from *centrally located* area of interest within the *centrally located* social stimuli. Raw data displayed. (c) Proportional Mean Dwell Time Percent (and standard error) to both the *centrally located* social areas of interest (within the *centrally located* social stimuli) and the *non-centrally located* social areas of interest (within the *non-centrally located* social stimuli). * = $p < 0.05$

To further investigate this finding, that overall WS individuals spend more time attending to *centrally located* social information and less time attending to *non-centrally located* social information, we ran post-hoc analyses in order to tease apart whether this could simply reflect a general slowing of eye movement in the WS group. A one-way ANOVA with Group (FXS, WS, CA-matched, MA-matched) as the between-groups factor was conducted on the Mean Time of First Saccade away from the central fixation point. A significant main effect was observed [$F_{(3, 80)} = 5.99$, $p = 0.001$, $n^2 = 0.18$]. Group comparisons revealed that the CA-matched control group (M = 237.30, SE = 11.42) was significantly faster to look away from the central fixation point compared to the WS group (M = 289.51, SE = 16.15, $p = 0.010$) and the MA-matched controls (M = 299.82, SE = 11.42, $p < 0.001$), but not the FXS group (M = 250.14, SD = 16.15, $p = 0.518$). The FXS group was also significantly faster to look away from the central fixation compared to the MA-matched controls ($p = 0.014$), but not the WS group ($p = 0.089$). These results suggest that the CA-matched controls and FXS individuals were quicker to look away from the central fixation than the MA-matched controls; but the WS group was only significantly slower than the CA-matched control group. Overall these results do not support the suggestion that the abovementioned WS findings could be explained purely by a reduction in eye movement speed.

Discussion

The current study was the first to manipulate the location of social information within naturalistic scenes to investigate the competing hypotheses of attentional capture and attentional disengagement in WS, while also taking into consideration general attentional engagement. Importantly, it is also the first study to date that has specifically explored the role that these different attentional mechanisms may play in processing social information within the FXS population.

Attentional Capture

The current findings did not provide any evidence to suggest attentional capture of social information in either FXS or WS. Specifically, the CA-matched control group displayed more evidence of relative attentional capture for socially salient information in comparison to both

clinical groups (particularly the WS group) as well as the MA-matched controls. This suggests that attentional capture for socially salient information is perhaps contingent on developmental level.

Our results are thus more consistent with those of Riby and Hancock (2009a, b) and Porter et al. (2010), who both found no evidence of attentional capture for social information in WS, rather than the findings of Tager-Flusberg and colleagues (2007). With regard to the discrepancies between these studies, it is of note that Tager-Flusberg et al. (2007) only found their significant difference in change detection ability between WS individuals and intellectually impaired matched controls when collapsing across three viewings of the same video. This may suggest that practice, rather than attentional capture by the social information, may explain the differences in results compared to our own and other more recent studies (Porter et al. 2010; Riby and Hancock 2009a,b). In other words, attraction to socially salient information (or newly familiar people) in the WS group may have occurred over time in the Tager-Flusberg et al. (2007) study, rather than pre-attentively, as would be suggested by an attentional capture hypothesis.

Attentional Disengagement

In contrast to the attentional capture hypothesis, the current finding did provide partial support for our attentional disengagement hypothesis. More specifically, as predicted, our FXS individuals were observed to disengage their attention from social information significantly faster than all other groups. However, our findings failed to provide significant evidence for the notion that WS individuals would take longer to disengage attention away from social information that was immediately available.

That our prediction about social attentional disengagement was not supported by the current findings is interesting in light of previous WS research, which has consistently reported difficulties with disengaging attention away from both social (e.g., Porter et al. 2010; Riby and Hancock 2008; Riby et al. 2009a) and non-social (e.g., Cornish et al. 2007; Lincoln et al. 2002) stimuli in the disorder. Having said this, the pattern of our results was in the predicted direction, with the WS group taking more time to disengage away from immediately available social information, albeit not significantly, than all other groups. This difference may not have reached

statistical significance due to a lack of power; or, alternatively, it may reflect the stimuli used in the current study.

More specifically, the initial fixation in all of our *centrally located* social stimuli was only ever presented directly over bodies of people; never over a face or, even more specifically, over an eye region of a person within the scene. Thus, we would suggest that the current findings concerning social attentional disengagement need to be treated with some caution, both because of the possible power limitation, and because results may have been different if the initial fixation was onto a face or an eye region. The latter possibility seems plausible due to the reported interest that individuals with WS have towards faces and eyes in particular (e.g., Mervis et al. 2003; Porter et al. 2010). That is, including more socially salient information at the immediate point of fixation may have led the current pattern to reach significance. Future research would benefit from manipulating the type of information underneath the point of first fixation (e.g., eyes, face, bodies) to determine whether the salience of the social information at fixation has an effect on the attentional disengagement difficulties observed in WS. One might, for example, predict the presence of a social salience effect.

The current findings with respect to social attentional disengagement in our FXS group were more unequivocal. Individuals with FXS were significantly faster to disengage their attention away from social information presented immediately, compared to all other groups; thus providing evidence in support of active avoidance of social stimuli by the FXS group. To date, this is the first eye-tracking study which has empirically investigated social avoidance in this way in FXS individuals by using naturalistic, albeit static, social scenes. The current results are consistent with anecdotal and observational reports of social avoidance within the FXS population, as well as the high rates of social anxiety reported in the disorder (Tsiouris and Brown 2004). Our findings are also commensurate with behavioral and eye-tracking studies which have focused specifically on direct eye-gaze in FXS. In more detail, Cohen and colleagues (1991) used a social interactional paradigm to reveal that FXS males displayed reduced eye-contact initiation with parents compared to individuals with autism. More recently, eye-tracking studies have revealed that

individuals with FXS show fewer fixations to, and spend less time looking at, the eye region of emotional faces compared to CA-matched controls (e.g., Farzin et al. 2009; 2011; Holsen et al. 2008; Cornish et al. 2004); and they spend a similar amount of time attending to the eye region as individuals with autism (Dalton et al. 2008).

Importantly, as mentioned above, when viewing the *centrally located* social scenes, our participants fixated initially on bodies of people rather than faces or eye regions. This may have reduced the aversive nature of the *centrally located* social stimuli for our FXS group, in which case, even more marked effects might have been seen if we had presented faces or eyes at fixation. This is because it is known that individuals with FXS find the eyes particularly aversive (e.g., Cohen et al. 1988; 1991; Dalton et al. 2008; Farzin et al. 2009; 2011).

Speculatively, the type of stimuli used may have implications for the performance of both FXS and WS individuals. As such, manipulating the first fixation location in future studies would allow us to investigate whether WS individuals would display more striking abnormalities in social attention and, in contrast, whether FXS individuals would display even more significantly active avoidance. For example, manipulating the first fixation on social information between bodies, faces, eyes and even different emotional facial expressions would allow us to determine whether avoidance/attraction of social information is based on salience, and whether what counts as 'salient' differs for our clinical groups. Importantly, future studies should also include manipulation of non-social information within the stimuli, particularly with respect to further delineating whether the disengagement difficulties observed in the WS individuals relates only to social information, or whether it is a more general attentional shifting deficit. Moreover, our finding that the WS group was not significantly slower to move their eyes from the central fixation compared to the FXS or MA-matched control groups suggests that the observed pattern of results cannot be purely explained by generally slower eye movements in the WS group. However, a more detailed investigation of potential intrinsic differences in eye movements will be of value in the future.

General Attentional Engagement

Our WS group spent significantly more time attending to social information when presented immediately at fixation compared to all other groups. Interestingly though, the WS group was found to spend less time attending to social information which was not immediately available, but only when compared to the CA-matched controls. Together with the finding that the WS group took longer, albeit not significantly, to disengage away from directly presented social information, this overall increase in attention to directly presented social information adds weight to the argument that attentional disengagement difficulties may play a role in the WS social phenotype (e.g., Mervis et al. 2003; Riby and Hancock 2009a). Moreover, the reduced overall attention given to social information presented in the periphery also provides indirect support against the attentional capture hypothesis.

Our prediction that the FXS individuals would spend significantly less time attending to social information overall, compared to the WS and control groups, was not supported. In fact, our FXS individuals attended to social information overall to a similar degree as the MA- and CA-matched controls. This latter finding seems inconsistent with the previous finding that our FXS group actively avoided the *centrally located* social information within the naturalistic scenes. However, we speculate that this initial avoidance of social information, combined with typical levels of attention to this information over time, may reflect some habituation to the social information over time. If so, this profile would be in contrast to socially anxious individuals who typically display a pattern of hypervigilance-avoidance, which involves initial hypervigilance towards a threatening stimulus followed by avoidance of that stimulus to reduce anxiety levels, which in turn hinders habituation (e.g., Mogg et al. 1997). We might speculate, however, in line with the *specificity hypothesis* (see Bogels and Mansell 2004), that, if more threatening social images had been used (those used in the current study had a mean valence of 5.54), or at least images more relevant to the concerns of our FXS individuals (e.g., emotional faces), the pattern of results may have differed; particularly as heightened social anxiety is often reported in FXS.

Manipulating the social information presented will be important in future studies, as will the inclusion of non-social control stimuli[4].

Limitations and Future Directions

Several limitations of the current study need to be considered when interpreting the findings. Firstly, the sample size in the current study, while similar to previous studies using eye-tracking paradigms in WS (Porter et al. 2010; Riby & Hancock 2008; 2009a, b) and FXS (Farzin et al. 2009; 2011; Shaw and Porter, 2012), was small and may have limited our power in detecting group differences, particularly given the heterogeneity in clinical populations such as WS and FXS. It also precluded us from investigating any potential sex differences within the groups. Future studies should endeavor to use larger sample sizes to allow for the exploration of how sex, chronological age, genotype, and level of cognitive ability may affect patterns of social attention. Moreover, this would also allow future studies to investigate possible associations between specific social attention characteristics and levels of social anxiety, ADHD and autistic features. Whilst not explicitly investigated in the current study, this is a valuable direction for future research particularly as social anxiety, ADHD, and autism are highly characteristic of FXS (e.g., Franke et al. 1998; Hatton et al. 2009; Rogers et al. 2001; Sullivan et al. 2006; Tsiouris and Brown 2004) and ADHD, generalized anxiety and specific phobias are common in WS (e.g., Dodd et al. 2009; Dykens, 2003; Leyfer et al. 2006). Of note, with respect to the current study, only one female FXS participant had a formal diagnosis of autism, based on parental report.

Another limitation of the current study was the use of two different standardized measures of general intelligence (WASI and WJ-R) to estimate the MA of our clinical groups. As the FXS cohort had participated in a larger battery of tasks, the WASI was used to minimize the amount of testing each participant endured. While it was not ideal to use different measures across the two clinical groups, we did not re-assess our WS group on IQ, as the IQ data had been collected less than 12 months prior. Importantly, both the WASI and WJ-R are well-standardized

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[4] Of note, there were no significant correlations between any visual scan-path parameters and either self-report ratings of social anxiety, or informant-report measures of autistic tendencies or ADHD symptomology in the FXS group.

tests of intellectual functioning and both have been documented to adequately and reliably estimate MA (Woodcock and Mather 1989; Psychological Corporation, 1999; Spreen and Strauss, 1998). Whilst no previous study has directly investigated the concurrent validity of these two measures, in general the WJ and Wechsler intelligence tests have consistently shown moderate-to-high correlations with each other across multiple versions (e.g., see Cummings 1994; Hess 2001; Schrank et al. 2010 for detailed reviews). Nevertheless, future research should aim to use the same battery across groups to ensure more direct and accurate comparisons. Moreover, as the current study's MA are based on measures that included both verbal and non-verbal abilities, our clinical cohorts' level of intellectual functioning and MA may be higher than that reported in previous FXS and WS studies, which tend to only use non-verbal IQ when matching with controls. Whilst this may make it difficult to compare results across studies, as the WASI and WJ-R both include verbal and non-verbal measures, we believe that the between groups comparisons made in the current study are informative in their own right.

The fact that the current study did not use multiple measures of visual attention is another potential limitation. Future research would benefit from, for example, correlating visual scan-paths with various neuropsychological measures of attention, as well as with ADHD symptomology. Perhaps, concurrent visual scan-path recording and neuroimaging recording to further explore the relationships between attention, visual scan-path patterns and neural activation would be even more informative. There have been limited studies investigating visual scan-paths and neurophysiological measures in both FXS and WS (Dalton et al. 2008; Holsen et al. 2008), and the few studies that do exist have found interesting differences between these clinical populations and controls. For example, compared to CA-matched controls, Dalton et al. (2008) found reduced fusiform gyrus activation in FXS individuals when performing a facial emotion discrimination task and, similarly, Holsen et al. (2008) found decreased activation in the medial and superior frontal cortices during successful face encoding in their FXS group. Moreover, amygdala activation in particular has been found to be abnormal in WS during emotional face processing tasks (Haas et al. 2009; Meyer-Lindenberg et al. 2005; Mobbs et al. 2004). In order to

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investigate potential brain abnormalities which may underlie the specific social attentional problems in FXS and WS, our focus should turn to methodologies which would allow for direct comparison of attentional processes in these syndromes whilst also measuring brain activation.

General Conclusion

This study is among the first to directly compare the role of attention in the processing of social information in FXS and WS individuals. The current empirical findings add to the growing body of evidence that suggests that individuals with WS display difficulties disengaging attention away from socially salient information; rather than having their attention captured by social information. With respect to FXS, the findings suggest that individuals with FXS actively avoid social information, at least initially. Importantly, however, our FXS group did attend to social information over time, unlike the pattern seen in socially anxious individuals.

In sum, our visual scan-path findings suggest diverging social attentional processes in FXS and WS individuals. With further research, these divergent patterns of social attention may lead us to a better understanding of the distinct social phenotypes that characterize these two neurodevelopmental disorders.

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Appendix 1

Individual Demographical Data for Clinical Participants

FXS Group	Gender	CA (yrs)	FSIQ	MA (yrs)	WS Group	Gender	CA (yrs)	FSIQ	MA (yrs)
fx001	Female	21.08	94	21.08	ws001	Female	33.66	48	6.75
fx002	Female	12.58	77	9.08	ws002	Male	20	45	7.92
fx003	Female	15.75	53	6.29	ws003	Male	16.33	76	9.5
fx004	Female	15.5	62	7.91	ws004	Male	25.83	54	9.33
fx005	Male	23.83	54	6.87	ws005	Male	22.33	70	10
fx006	Female	38.08	59	7.37	ws006	Female	11.42	51	6.25
fx007	Female	18.58	54	6.75	ws007	Male	13.83	70	6.66
fx008	Female	20.83	56	7.29	ws008	Male	20.66	45	8.08
fx009	Female	23.83	52	6.05	ws009	Male	16.58	43	6.42
fx010	Female	19.5	56	7.16	ws010	Male	37	48	6.42
fx011	Male	51.42	58	6.16	ws011	Female	11.66	54	6.16
fx012	Female	12.08	96	11.25	ws012	Male	37.42	41	7.27
fx013	Female	27.16	57	7.05	ws013	Female	24.58	81	11.08
fx014	Female	21.92	69	11.08	ws014	Female	19.25	61	8.75

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Chapter 4 – Emotion Recognition and Visual-Scan Paths in Fragile X Syndrome

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Emotion Recognition and Visual-Scan Paths in Fragile X Syndrome

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Abstract

This study investigated emotion recognition abilities and visual scanning of emotional faces in 16 Fragile X syndrome (FXS) individuals compared to 16 chronological-age (CA-) and 16 mental-age (MA-) matched controls. The relationships between emotion recognition, visual scan-paths and symptoms of social anxiety, schizotypy and autism were also explored. Results indicated that, compared to both control groups, the FXS group displayed specific emotion recognition deficits for angry and neutral (but not happy or fearful) facial expressions. Despite these evident emotion recognition deficits, the visual scanning of emotional faces was found to be at developmentally appropriate levels in the FXS group. Significant relationships were also observed between visual scan-paths, emotion recognition performance and symptomology in the FXS group.

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Emotion Recognition and Visual-Scan Paths in Fragile X Syndrome

Individuals with Fragile X syndrome (FXS) display a wide range of social difficulties in everyday life such as symptoms of social anxiety, autistic asociality and idiosyncratic traits of schizotypal personality disorder. In recent years, there has been an interest in better understanding the causes of these social difficulties, including whether abnormalities in the visual processing of emotional facial expressions in FXS (Dalton et al. 2008; Farzin et al. 2009; Holsen et al. 2008) might explain some of the social difficulties that these individuals face. While several studies have attempted to explore this research question, the findings remain unclear (e.g., Holsen et al. 2008). Additionally, no study to date has investigated the relationship between the visual processing of emotional faces and explicit emotion recognition in the FXS population. The aim of the current study was to elucidate further the way in which emotional facial expressions are visually processed by individuals with FXS and how this processing might impact on the nature of any observed emotion recognition problems. Relationships between explicit emotion recognition, visual scan-paths and the FXS social-behavioral phenotype (e.g., social anxiety, autism and schizotypal personality disorder) are also explored.

FXS not only causes social difficulties, but it is also the most common hereditary cause of cognitive impairment (Mazzocco et al. 1994). FXS results from large expansions of the cytosine-guanine-guanine (CGG) trinucleotide repeat in the promoter region of the fragile X mental retardation 1 (FMR1) gene (Frankland et al. 2004; Hatton et al. 2006). In individuals with > 200 CGG repeats, the FMR1 gene is silenced and interrupts the production of FMR1 messenger RNA (Verkerk et al. 1991). This interruption results in the failure to produce fragile X mental retardation protein (FMRP) (Hagerman 2002; Tassone et al. 2000), which in turn leads to the collection of features that comprise the FXS phenotype (Mazzocco and Reiss 1999).

Intellectual impairment is one of the most prominent cognitive symptoms associated with FXS (e.g., Lewis et al. 2006; Mazzocco 2000; Tamminga and Huber 2007). Due to the X-linked nature of the disorder, males tend to be more severely affected with FXS affecting approximately 1 in 4000 males and 1 in 8000 females (Sherman et al. 2002; Turner et al. 1996a). IQ typically ranges from

severely impaired to mild-to-moderately impaired. For females, IQ can fall anywhere between the severely impaired to average range (Hagerman 2002). In addition to general intellectual impairment, FXS is associated with more specific areas of cognitive strength and weakness. The FXS cognitive profile is typically characterized by relative deficits in visuospatial and visuoconstructional skills, mathematics, short-term memory and higher-order thinking (e.g., Mazzocco 2001); as well as inattention, often severe enough to warrant a diagnosis of attention-deficit hyperactivity disorder (ADHD) (see Hagerman 2002). On the other hand, verbal skills, such as expressive vocabulary and language comprehension, remain a relative strength (e.g., Pennington and Bennetto 1998).

The FXS social-behavioral phenotype is of most interest to the current paper. This includes significant social impairments, including social anxiety and withdrawal, gaze aversion, reduced interaction with peers, unusual responses to sensory stimuli, as well as, schizotypal personality and autistic features (e.g., Cohen et al. 1989; Cohen et al. 1991; Cornish et al. 2001; Hessl et al. 2001). The incidence of co-morbid autism, social anxiety and schizotypal personality disorder is higher in FXS compared to the typically developing population (Franke et al. 1996; Rogers et al. 2001; Tsiouris and Brown 2004).

Social Deficits in FXS

Social anxiety. Parents often report social anxiety as one of the most debilitating features experienced by their child with FXS. Not surprisingly then, research has shown that a social anxiety disorder is one of the most common co-morbid diagnoses in both males and females with FXS. The frequency and severity of social anxiety is higher in females with the full-mutation compared to the premutation (Franke et al. 1996; Tsiouris and Brown 2004), suggesting a genotype-phenotype relationship. In fact, Franke and colleagues (1996) reported that mothers with the FXS full-mutation were three to four times more likely to have a clinical social anxiety diagnosis than premutation mothers.

Schizotypal personality disorder. Schizotypy refers to a spectrum of personality traits, such as limited capacity for close relationships, eccentric behaviors, as well as odd and unusual perceptions and thinking (American Psychiatric Association 2000; DMS-IV-TR) which can be seen, to

varying degree, in the general community. These traits are also observed, at more extreme levels, in schizotypal personality disorder (SPD), which is considered to be on the lower end of the clinical schizophrenia spectrum; with an abundance of research indicating a genetic relationship between SPD and schizophrenia (e.g., Kendler et al. 1993). Research in FXS has shown that females with the disorder display significantly higher rates of schizotypy compared to familial and intellectually impaired control groups (Sobesky et al. 1994). Additionally, SPD has been reported to be the most prominent DSM-IV Axis II diagnosis, with 76.9% of FXS females meeting criteria for diagnosis of SPD in one study (Franke et al. 1996) and similar prevalence rates observed in males with FXS (see Kerby and Dawson 1994). This is in contrast to the prevalence rate for SPD of approximately 1% in the general population (Torgersen et al. 2001).

Autism. Approximately 15-25% of individuals with FXS have a comorbid diagnosis of autism (Hagerman et al. 1986; Hatton et al. 2002; Mineur et al. 2006; Rogers et al. 2001). Another 50-90% of FXS individuals are reported to be on the autism spectrum (Rogers et al. 2001). As such, autistic features such as echolalia and perseverations, hand flapping and biting, delayed imitative and symbolic play, language delay, poor eye contact, and poor social relatedness with unfamiliar people are common in FXS individuals (Fryns et al. 1984); even in those described as socially responsive (Bregman et al. 1988). While the abnormal social interactions in FXS appear, at face value, similar to those seen in individuals with idiopathic autism (Garner et al. 1999), many researchers have speculated that the underlying mechanisms of poor social interaction may differ between the two disorders (Kaufmann et al. 2004; Sudhalter and Belser 2001). For example, Cohen and colleagues (1988; 1991) reported that males with FXS differed from males with idiopathic autism in that the former: (1) avoided strangers but not parents (Cohen et al. 1989) and (2) avoided eye contact with parents compared to males with autism who made eye contact after the parent's initial attempt (Cohen et al. 1991).

Social impairments are characteristic of individuals with social anxiety, schizotypal personality disorder and autism; impacting significantly on the daily lives of individuals with these conditions. While there are similarities in the social impairments observed across these disorders,

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the underlying nature of these deficits remains unclear. For example, Cath and colleagues (2008) asserted that, while there is marked overlap between the social contact and communication problems seen in autism and social anxiety disorder, there may be fundamental differences in the cognitions that underlie these behaviors (see Cath et al. 2008 for discussion). Another example of such a distinction may occur in relation to emotion processing abilities. While all three disorders display some degree of emotion processing difficulty, particularly with respect to processing emotional facial expressions, there are variations within and across disorders.

Facial Emotion Recognition

Researchers have suggested that faces may represent an exceptional class of stimuli for humans (Farah et al. 1998); with newborns displaying preferential behavior towards face stimuli from as early as a few days old (e.g., Morton and Johnson 1991). The ability to recognize facial expressions and, therefore, gain socially relevant information is a fundamental requirement for normal reciprocal social interactions. The eyes are thought to be particularly important for understanding complex mental states (Baron-Cohen and Cross 1992) and effectively convey the emotional state of our fellow humans. There is evidence that individuals with social anxiety (e.g., Simonian et al. 2001), schizotypal personality disorder (e.g., Mikhailova et al. 1996) and schizophrenia (see Edwards et al. 2002), as well as autism (e.g., Celani et al. 1999; Pelphrey et al. 2002), display emotion recognition problems. While specific causes of these deficits remain rather unclear, there is evidence to suggest that all three disorders have particular difficulties with negative emotional expressions

For example, socially anxious individuals reportedly display a negative bias in interpreting emotional expressions (Rapee and Heimberg 1997) and heightened sensitivity for negative, or potentially threatening, emotional expressions (Veljaca and Rapee 1998). In contrast, in schizophrenia and schizotypal personality disorder, deficits, in contrast to biases, are seen for correctly identifying negative (particularly fear) emotional expressions as compared to positive emotions (Poreh et al. 1994; Mikhailova et al. 1996). Similarly, individuals with autism have been reported to display specific negative emotion recognition deficits (Humphreys et al. 2007; Pelphrey

et al. 2002). Deficits for happy emotional expressions have also been reported in individuals with autism (Celani et al. 1999) and some researchers have even reported intact emotion recognition abilities (Adolphs et al. 2001; Ozonoff et al. 1990).

Social anxiety, schizotypy and autism are commonly reported in FXS (Hagerman 2002). Moreover, there is growing evidence that individuals with FXS may also display some degree of emotion recognition difficulties (Cornish et al. 2005; Hagan et al. 2008). As such, the social anxiety, schizotypy and autistic features seen in FXS may associate with any emotion recognition deficits seen in FXS. To date the relationship between these social features of FXS and emotion recognition abilities in FXS have not been explored.

Facial Emotion Recognition in FXS

Early research suggested that there was no obvious deficit in FXS for basic recognition of the six universal emotions (anger, disgust, fear, happy, sad and surprised), whether in adult males with FXS (Simon and Finucane 1996) or adult females with FXS (Mazzocco et al. 1994), compared to typically developing control groups. Similar results have also been reported in children with FXS (Turk and Cornish 1998; Wishart et al. 2007). However, the majority of these earlier studies employed simple picture-to-picture matching paradigms, where participants were asked to match the target emotional face to photos or schematics of emotional faces. Consequently, to successfully complete these picture-to-picture paradigms one does not need to use knowledge of emotions; rather one can rely solely on matching perceptual features (i.e., matching stimulus to target based on similar upward-turned mouths, without identifying, for example, that a particular facial expression is indicative of a happy emotional state. As such, these tasks are perhaps not ideal for examining the processes that individuals undertake when determining the facial emotional expression in day-to-day life (see Hobson 1991 for discussion).

In contrast, Cornish and colleagues (2005) used tasks of emotion recognition that required participants to label expressions and found evidence for emotion recognition deficits in adult FXS male carriers compared to well-matched familial and non-familial typically developing control groups. Results indicated that the FXS carriers performed significantly worse than both control

groups. The deficit was most noticeable for neutral faces, remaining even after statistically controlling for IQ (Cornish et al. 2005). Unfortunately, analyses of error patterns were not conducted to determine whether a negative bias was present in line with the patterns observed in socially anxious individuals (Rapee and Heimberg 1997). Consistent with Cornish et al.'s (2005) results, Hagan and colleagues (2008) also reported that females with the FXS full mutation were significantly worse than typically developing controls at recognizing neutral, but not happy or sad faces; and this impairment was associated with disruptions to face-processing neural networks (Hagan et al. 2008).

This emerging evidence of emotion recognition impairments or biases, albeit from two studies, raises questions about the emotion recognition abilities of individuals with FXS. This past research, together with the overwhelming presence of characteristics of social anxiety, schizotypy and autism in FXS (all of which associate with some degree of emotion recognition deficit in individuals without FXS), suggests that these individuals' ability to process emotional faces may be more impaired than once thought. It is important, therefore, to determine whether individuals with FXS do display emotion recognition deficits, and if so, whether the pattern of deficits is similar or different to that seen in social anxiety, autism and schizotypal personality disorder.

Visual Scan-paths

One's ability to accurately recognize emotional facial expressions is contingent upon the manner in which the face is processed. That is, while salient facial features (e.g., smiling mouth) may be important for emotion recognition, configural cues have been found to be more significant (Calder and Jansen 2005). For example, research suggests that typically developing adults recognize facial expressions by attending to the internal facial features in a holistic manner, attending to the eyes, nose and mouth in an "upside-down triangle" configuration (Calder and Jansen 2005; Pelphrey et al. 2002); first attending to the eyes and then the mouth (e.g., Tanaka and Farah 1993). While in the past it was quite difficult to assess the manner in which individuals processed facial expressions of emotion, the development of eye-tracking equipment has made it easier to investigate typical or aberrant emotional face processing in clinical populations. Abnormal visual

scan-paths have been reported in many developmental and psychiatric disorders, such as ADHD (e.g., Marsh 2008), Williams syndrome (WS; Porter et al. 2010), and patients with acquired brain lesions to the amygdala and frontal lobes (e.g., Adolphs et al. 2005). Notably, abnormal face scan-paths have also been observed in social anxiety, autism and schizophrenia.

For example, reduced fixations to salient facial features (eyes, nose, mouth) have been observed in individuals with social anxiety (Horley et al. 2003; 2004), autism (e.g., Dalton et al. 2005; Pelphrey et al. 2002) and schizophrenia (e.g., Green et al. 2003). Individuals with social anxiety have also been reported to display increased scan-path duration, suggesting a pattern of hypervigilance, and avoidance, indexed by reduced fixations (Horley et al. 2003; 2004); whereas individuals with schizophrenia display a 'staring' pattern of avoidance (e.g., Loughland et al. 2004) and individuals with autism are observed to exhibit an "erratic" and "disorganized" pattern of scanning characterized by scanning a select few and unimportant facial features (Pelphrey et al. 2002). Abnormal face scanning in social anxiety and schizophrenia has been reported to be particularly apparent for negative expressions (Green et al. 2003; Horley et al. 2003; 2004). No studies have explicitly investigated face scan-paths as a function of emotional expression in individuals with autism. Nevertheless, eye avoidance has been found to be associated with emotion recognition difficulties in autism (Pelphrey et al. 2002), as well as with abnormal brain functioning (particularly in the amygdala; Dalton et al. 2005) and reduced socialization, as indexed by the socialization domain of the Vineland Adaptive Behavior Scales Expanded Edition (Klin et al. 2002).

While there has been a large volume of eye-tracking studies published on social anxiety, schizophrenia and autism, there has been limited research using eye-tracking to investigate emotion processing in FXS. Of those studies that have been conducted, none have specifically investigated how high levels of social anxiety, schizotypy and autism in FXS participants may affect both emotion recognition and face scan-paths in these individuals.

Visual scan-paths in FXS

Dalton and colleagues (2008) went a step further than a simple eye-tracking study and simultaneously recorded brain activation (fMRI) and eye-gaze fixations to compare individuals with

FXS and idiopathic autism on a facial emotion discrimination task (i.e., identify whether an emotion is present or not). Results showed that the FXS group displayed a similar yet less aberrant pattern of gaze fixations compared with the autism group, relative to a control group. Specifically, there were no significant group differences in fixations to the eyes, but marginally reduced fixations to the eyes in the autism group compared to the typically developing controls. In terms of neural activation, results indicated a unique underlying neural circuitry in individuals with FXS (without a comorbid autism diagnosis) compared to both typically developing controls and individuals with idiopathic autism. The FXS group displayed fusiform gyrus hypo-activation compared to typically developing controls; and significantly greater activation in the left hippocampus, left superior temporal gyrus, left postcentral gyrus and right insula than both typically developing and autistic individuals. This supports the hypothesis that autistic characteristics in FXS and idiopathic autism are not identical. However, these authors did not specifically explore whether FXS individuals with more autistic symptomatology processed emotional faces more similarly to those non-FXS individuals with idiopathic autism.

To further explore abnormal neural circuitry in FXS, Holsen and colleagues (2008) investigated brain activation levels during a fearful face encoding task and related performance to social anxiety levels. Compared to typically developing chronological-age (CA-) matched controls, the FXS group displayed poorer memory for previously seen fearful faces, significantly reduced eye and face fixations, and a unique pattern of neural activation. Specifically, the FXS group displayed decreased activation in the medial and superior frontal cortices during successful face encoding. Additionally those FXS individuals who displayed higher levels of social anxiety, as measured by the Social Phobia and Anxiety Inventory (SPAI; Turner et al. 1996b), showed less neural activation in fronto-social cognition regions and hippocampal memory areas when encoding emotional faces that they later remembered (Holsen et al. 2008). These researchers concluded that social anxiety in FXS is likely related to dysfunction in neural networks associated with processing of social information. However, this study used only fearful facial expressions and no explicit emotion recognition task was performed, so it is unclear whether a specific deficit in recognizing fearful

expressions was apparent, or whether the observed neural dysfunction would generalize across other emotional expressions.

Farzin and colleagues (2009) used eye-tracking to investigate fixations and pupil size responses in a group of adolescents and young adults with FXS as they viewed photographs of calm, happy and fearful facial expressions, as well as scrambled faces. Results indicated that, compared to typically developing CA-matched controls, individuals with FXS made fewer fixations to, and spent less time looking at, the eye region of faces. They also displayed increased pupil size reactivity to emotional faces, which the authors argued was suggestive of hyperarousal and heightened anxiety. Moreover, pupil dilation in response to the fearful faces was negatively correlated with the number of fixations to the eyes of all faces. This pattern was observed in both males and females with FXS, was not significantly associated with severity of autistic symptomology, and has been shown to be consistent over time (Farzin et al. 2011).

Overall, FXS eye-tracking studies have reported reduced fixations to, and less time spent attending to, the eyes of emotional faces, compared to typically developing CA-matched controls (Dalton et al. 2008; Farzin et al. 2009; 2011; Holsen et al. 2008). These findings parallel those seen in autism (Dalton et al. 2005; Klin et al. 2002; Pelphrey et al. 2002; Riby and Hancock 2008), schizophrenia (Marsh and Williams 2006) and social anxiety (Horley et al. 2003; 2004). However, these findings are difficult to interpret without a mental age- (MA-) matched control group. The inclusion of a MA-matched control group is important, since there is evidence suggesting that the accuracy of visual scanning and voluntary control of eye movements (Fukushima et al. 2000; Whiteside 1974), as well as improvements in facial recognition (Pimperton et al. 2009) and configural processing of emotional faces (Durand et al. 2007), increase throughout childhood, adolescence and early adulthood. These findings suggest that the visual scanning of emotional faces may also be refined over time. As such, to determine whether scanning of emotional faces in FXS is abnormal, FXS participants need to be compared to a MA-matched control group.

It also remains unclear from the studies reported to date whether the individuals with FXS accurately recognized the emotional expressions that were displayed during these previous eye-

tracking experiments. While aberrant visual scanning of emotional faces and emotion recognition deficits in FXS have been reported separately in the literature, it is difficult to determine the implication of these previous separate findings without exploring visual scanning and emotion recognition concurrently. Exploring the relationship between explicit emotion recognition ability, visual scan-paths (particularly reduced fixations to the eyes) and levels of autism, social anxiety and schizotypal personality disorder symptomology could also provide directions for further research and potentially aid in developing treatments and remediation programs.

Study Aims

This study aimed to investigate emotion recognition and visual scanning of emotional facial expressions (neutral, happy, angry and fearful) in FXS individuals compared to two typically developing control groups, one matched to the FXS group on CA, and the other matched on MA. In line with previous research (see, e.g., Hodapp, Burack and Zigler 1990; Leonard 1998), these two control groups were chosen in order to tease apart the influence of IQ on emotion recognition abilities or visual scanning. That is, if the FXS group is impaired compared to the CA-matched control group, but not compared to the MA-matched control group, this would indicate that differences in emotion recognition or visual scan-paths are due to developmental delay rather than intellectual disability. If, by contrast, the FXS group are impaired compared to both CA- and MA-matched controls, then this pattern would suggest that differences in IQ may be driving the results, or otherwise developmental deviance. The relationships between emotion recognition, scan-paths and symptoms of social anxiety, schizotypy and autism were explored.

Due to the inconsistencies seen in the emotion recognition literature on FXS (e.g., Cornish et al. 2005; Hagan et al. 2008; c.f. Turk and Cornish 1998; Wishart et al. 2007) and the emerging evidence of aberrant processing of emotional faces in FXS (Dalton et al. 2008; Farzin et al. 2009; 2011; Holsen et al. 2008), this paper had three specific objectives. The first objective was to investigate whether individuals with the FXS full mutation have emotion recognition difficulties using a forced-choice emotion labeling paradigm. It was predicted that the FXS population would show: (1a) a specific emotion recognition deficit for negative (angry and fearful) emotional facial

expressions; as well as (1b) a pattern of deficits consistent with negative bias, characterized by misidentifying ambiguous (neutral) facial expressions as negative (angry or fearful).

The second objective was to investigate how individuals with FXS visually scan emotional faces, and whether this pattern of visual scanning differed as a function of emotional expression of a face. It was predicted that, compared to MA- and CA-matched controls, individuals with FXS would: (2a) take longer to initially fixate on the eye region (initial avoidance of eyes); (2b) attend less to the eye region overall, particularly for negative emotional expressions (general eye avoidance for negative expressions); and (2c) scan emotional faces in a qualitatively different manner. The third objective of this study was to extend the previous research into emotional face processing in FXS by investigating the relationship between emotion recognition and visual scan-paths. It was predicted that: (3) poorer emotion recognition would be associated with aberrant visual scan-paths.

The final objective was to determine whether emotion recognition ability and patterns of visual scanning were related to MA, CA and also self- and parent-report indices of social anxiety, schizotypy and autism features. Correlational analyses investigated these relationships. It was predicted that: (4a) poorer emotion recognition would be associated with aberrant visual scan-paths; and (4b) higher ratings of social anxiety, schizotypy and autism would be associated with both poorer emotion recognition and more aberrant visual scan-paths.

Method

Participants

Participants were 16 FXS individuals, 16 CA- and gender-matched typically developing controls, and 16 MA- and gender-matched controls. All participants displayed normal or corrected to normal vision.

Fragile X syndrome 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 (4 male; 12 female). All FXS participants exhibited the medical and clinical phenotype associated with FXS and genetic testing confirmed the characteristic >200 CGG repeats

associated with the disorder (6 Southern Blot, 10 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 FXS cohort fell in the mildly impaired range and was consistent with the average level of intellectual disability reported in the literature.

Typically developing control participants. CA- and MA-matched controls were recruited through the Macquarie University Kids' Science Club and via advertisements distributed across the Macquarie University campus. Exclusion criteria were a history of learning difficulties, developmental delay, intellectual impairment, as well as behavioral, psychological, sensory or cognitive deficits or a history of neurological compromise. Details regarding CA, MA and FSIQ for both CA- and MA-control groups are reported in Table 1.

Table 1

CA, MA and FSIQ by group

	FXS Group	MA-matched Group	CA-matched Group
	Mean *(SD)* Range	Mean *(SD)* Range	Mean *(SD)* Range
N	16	16	16
% females	75%	75%	75%
CA [a]	24.8 *(12.9)* 12.1 – 56.1	8.3 *(3.5)* 5.9 – 20.3**	24.5 *(12.4)* 12.1 – 53.1
MA [a]	8.4 *(3.8)* 6.0 – 21.1	9.2 *(3.5)* 6.5 – 20.3	24.5 *(12.4)* 12.1 – 53.1**
FSIQ [b]	64 *(13.7)* 51 – 96	106 *(8.6)* 94 – 126**	109 *(10.1)* 91 – 128**

[a] Mean CA and MA in years
[b] FSIQ = Standard Score (mean = 100, SD = 15)
Significant difference between FXS group and relative control group at: * = $p \leq 0.05$; ** = $p \leq 0.01$

Materials

Facial stimuli. Facial stimuli for both the visual scan-path and emotion recognition experiments included six identities from the Ekman standardized face set (IDs 1, 2, 7, 8, 9, & 13; Ekman and Friesen 2003). These stimuli have been deemed reliable representations of individual emotional expressions and have been widely used in the emotion and face processing literature (see Palermo and Coltheart 2004 for a review). More specifically, they have been used with a wide range of neurodevelopmental disorders (Pelphrey et al. 2002; Porter et al. 2010). Each identity's neutral, happy, angry and fearful facial expressions were used; resulting in a total of 24 face presentations (six of each emotion, with an equal number of male and female faces).

Social Phobia and Anxiety Inventory (SPAI). The SPAI adult (Turner et al. 1996b) and child (SPAI-C; Beidel et al. 1998) versions were used to assess the frequency and range of social anxiety. The SPAI is a self-report measure designed to assess somatic, cognitive and behavioral symptoms of social anxiety. The SPAI is validated for individuals 14 years and over, consisting of 45 items rated on a seven-point Likert scale (ranging from 0 = 'never' to 6 = 'always'). A social phobia-agoraphobia difference score of 60 or above indicates possible social anxiety (Turner et al. 1996b). The SPAI-C is designed for children aged 8 to 14 years and is comprised of 26 items rated on a three-point Likert scale (with 0 = 'never, or hardly ever', 1 = 'sometimes', and 2 = 'most of the time, or always'. Both the SPAI and SPAI-C have demonstrated good convergent validity with self-report and behavioral measures of social anxiety (Beidel et al. 1998). They have also been used successfully in previous studies of self-reported levels of social anxiety in FXS (Holsen et al. 2008; Lesniak-Karpiak et al. 2003). The child and adult versions of the SPAI are not directly comparable; as such, to allow for comparison between children and adults in the current study z-scores were calculated for each individual based on the difference score (SPAI) or total score (SPAI-C) as per Holsen et al. (2008). Three FXS male participants failed to complete the SPAI(-C) due to difficulties understanding the questions; and one CA-matched male control failed to return the SPAI(-C).

Schizotypy Traits Questionnaire (STA). The STA is a self-report questionnaire measures schizotypy using three different scales: (1) Magical Thinking, (2) Unusual Perceptual Experiences

and (3) Paranoid Ideations/Social Anxiety. Versions of the STA have been used previously with typically developing adults and children (Cyhlarova and Claridge 2005; Rawlings and MacFarlane 1994) and have been reported to be valid and reliable measures of individual features of schizotypal personality as well as psychosis proneness (Raine 1991). The current study used the children's version of the STA (see Cyhlarova and Claridge 2005) in order to avoid comprehension difficulties in the FXS participants and MA-matched controls, and included the original adult wording in parentheses (as per Claridge and Broks 1984) in order to ensure relevance to the higher functioning FXS participants and CA-matched controls.

An additional scale was also included to better measure 'anhedonia', a DSM-IV feature of schizotypy not fully assessed in the STA. The Introverted Anhedonia (IA) scale of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason et al. 1995) was thus included to measure social and physical anhedonia. The IA scale was combined with the STA questionnaire, resulting in four subscale scores (the three STA subscales and the IA subscale) and a total score (including the O-LIFE IA score) for all participants. Two FXS male participants failed to understand the questionnaire and as such did not complete it. Again, one CA-matched male control failed to complete the STA questionnaire.

Autism Behavior Checklist (ABC). The ABC is an autism screening checklist that is part of a broader tool, the Autism Screening Instrument for Educational Planning, second edition (ASIEP-2; Krug et al. 1993). The ABC is a parent-report measure designed to assess autism in both children and adults and includes 57 behavioral characteristics of autism divided into five categories: (1) Sensory, (2) Relating, (3) Body and Object Use, (4) Language, and (5) Social and Self Help. The ABC is appropriate for children and adults with mental ages from 3 years and above, which covers the age range of the current participants. A cut-off score of 64 or higher is suggestive of autism; although it is not diagnostic. The ABC has been previously used with FXS individuals (e.g., Hagerman et al. 1986). There was missing data for one FXS female participant and one CA-matched male control participant; due to their informant failing to return the questionnaire.

Wechsler Abbreviated Intelligence Scale (WASI). The WASI is a commonly used short and reliable measure of intelligence (Sattler 2001) consisting of four subtests (Vocabulary, Similarities, Block Design and Matrix Reasoning), which take approximately half an hour to administer. It has been used previously with individuals with intellectual impairments (e.g., Agnew and Powell 2004), including FXS (Garcia-Nonell et al. 2008; Hessl et al. 2008). There are published WASI norms for individuals between 6 and 89 years of age and MA can be estimated by use of Table A.7 in the manual. Of note, one FXS male (6.3%) performed at floor on the WASI; thus his MA may be overestimated.

General Procedure

The general experimental procedure for the eye-tracking and emotion recognition portion of the experiment was identical to that of Porter et al. (2010), who investigated emotion recognition abilities and visual scanning of faces in WS. In brief, participants were seated in a darkened room in a comfortable chair and viewed the face images on a Dell 16" CRT monitor from a distance of 60 cm (viewing distance controlled by seat position). Images were presented at a standard size of 10.5 cm (406 pixels) wide by 16.0 cm (599 pixels) high, creating a horizontal visual angle of 10.0° and a vertical visual angle of 15.2°.

In line with previous visual scan-path research in other clinical populations, such as schizophrenia (Green et al. 2003) and autism (Pelphrey et al. 2002), participants first viewed the facial expressions passively while their scan-path patterns were recorded. Following this, participants completed the emotion recognition task without eye movement recordings. Visual scan-paths were thus recorded during passive viewing, and during the first exposure to each face. Although Pelphrey and colleagues (2002) showed no differences in visual scanning when participants passively-viewed emotional faces compared to when they completed an emotion recognition task, other research has shown that adding a cognitive task can significantly alter gaze behavior via top-down attentional processes (e.g., Hayhoe and Ballard 2005). As such, visual scan-paths were not recorded while participants made emotion judgments, to ensure the accuracy of scan-path recordings. Images were displayed in the same pseudo-randomized order for both the

visual scan-path and the emotion recognition parts of the experiment. All participants completed both tasks in a single session, which lasted approximately 30 minutes, including a short break. Behavioral and intelligence measures were collected at a second session for all participants, as part of a larger battery of tasks.

Visual scan-path experiment procedure. Eye movements were recorded using the Eyelink-II gaze monitoring system (SR Research Ltd.), sampling at a temporal resolution of 500 Hz and with a spatial resolution of 0.2°. An eye movement was classified as a saccade when its distance exceeded 0.2° and velocity reached 30°/s, or when its length exceeded 0.2° and its acceleration had reached 8000°/s^2.

The head-mounted apparatus used to record eye-movements was adjusted to obtain binocular eye movements. Prior to the experiment, a nine-point calibration of eye fixation position relative to the screen was conducted. Participants viewed a centrally placed black dot (10mm in diameter) which moved to eight locations around the periphery and center of the screen. Participants were asked to fixate on the central dot and track its movements with their eyes. The dot moved to a new location once the computer had recorded an adequate corneal 'lock' from the participant (at least 1,000ms viewing in each position). A successful calibration meant that a robust fixation recording could be obtained across the entire width and breadth of the computer screen. The experimental procedure only proceeded once a satisfactory calibration was achieved. The initial point of retinal attention was controlled by a black dot presented centrally for 1,000ms immediately prior to each face stimulus.

Participants passively viewed the faces as they were presented in a pseudo-random order for 10,000ms each. Before the image was presented, participants fixated for 1,000ms on a central fixation dot to ensure that all participants were attending to the same part of the screen when the face stimulus appeared. After 10,000ms the face was again replaced by the fixation dot. Manual experimenter control initiated the next trial.

Visual scan-path parameters. Visual scan-path parameters included: (1) Mean Time to First Fixation (MTFF), which refers to the mean length of time (in milliseconds) for the first fixation to

enter the current area of interest (AOI: see below for further clarification); (2) Mean Fixation Percent (MFP), which refers to the mean percentage of fixations made in each AOI; and (3) Mean Dwell Time Percent (MDTP), which refers to the mean percentage of time spent fixating in each AOI. The patterns of results were similar for the MFP and MDTP data, so only the latter is reported here.

Defining areas of interest (AOIs). Regions of interest were drawn for each facial image using the drawing functions provided in the EyeLink DataViewer. Six AOIs were delineated including 'left eye', 'right eye', 'brow', 'nose', 'mouth', and 'other' internal facial regions (see Figure 1 for graphic representation of defined AOIs). The 'other' internal facial region was calculated as whole face (traced around the hairline) minus the other five interest areas. We were primarily interested in the eye region as a whole; as such we summed the data over the eyes and brow regions ("eye region"). To ensure no lateralization effects were present, independent group ANOVAs comparing MDTP to the left eye and right eye found no significant differences. Thus, the analyses below used AOIs defined as: (1) 'eye region'; (2) 'nose'; (3) 'mouth'; and (4) 'other' internal facial regions (e.g., cheeks, forehead, and hairline excluding hair).
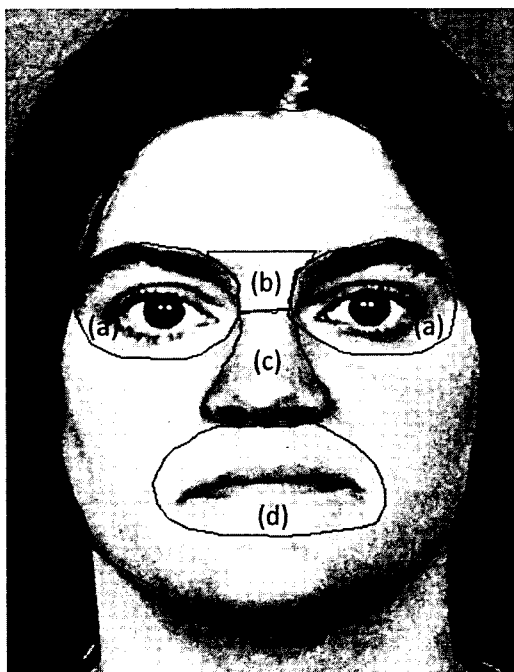

Figure 1. Example of AOIs: (a) = Eye; (b) = Brow; (c) = Nose; (d) = Mouth; (a) and (b) = Eye Region

Emotion recognition procedure. The same images used in the visual scan-path experiment were displayed for a second occasion in the same pseudo-randomised order. Participants were requested to verbally label the expression displayed in a forced choice paradigm. To reduce the load on working memory all participants were given a written list of each possible option ('happy', 'scared', 'angry' and 'normal')[1], and the investigator also read the list aloud on each trial. Participants were given an unlimited time to respond, with the image remaining on screen until a response was made.

Results

For all analyses a *p* value of 0.05 was used to indicate significance in order to minimize the possibility of Type II error (see Rothman, 1990). One face image was excluded from all analyses (emotion recognition and visual scan-path: ID 13, neutral expression), due to the significantly high number of incorrect emotion recognition responses across all groups[2]. This left a total of 23 images (six of happy, fearful and angry; and five neutral) in the following analyses.

Emotion Recognition

To investigate possible group differences in emotion recognition ability, a repeated measures analyses of variance with Group (FXS, CA-matched and MA-matched) as the between subject factor and Emotion (neutral, happy, angry and fearful) as the within subjects factor on mean percent correct was conducted. Results showed significant main effects for both Group [F (2, 45) = 7.82, p = 0.001, η^2 = 0.26] and Emotion [F (3, 135) = 6.71, p = 0.001, η^2 = 0.13], and a significant Group by Emotion interaction [F (6, 135) = 2.70, p = 0.028, η^2 = 0.11]. The significant interaction resulted from the FXS group performing significantly worse than both the CA-matched and MA-matched controls in their ability to recognize neutral (p's ≤ 0.012) and angry (p's ≤ 0.007) expressions. They were also significantly worse at recognizing fearful expressions compared to CA-

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[1] 'Normal' was used rather than 'neutral' on the written response list due to a large number of young controls reading neutral as normal during piloting. Verbal task instructions, however, were given to all participants prior to beginning the emotion recognition task explaining the four choices as: *happy, scared, angry, and neutral – a normal or blank face with no expression).*

[2] 65% of all participants (FXS: 68.8%; CA-matched controls: 56.3%; MA-matched controls: 73.3%, p = 0.536) failed to correctly label this image as neutral; over 90% of errors judged the face to be angry.

matched controls (p = 0.008), but not MA-matched controls (p = 0.290; see Figure 2a). To ensure

that these results were not being driven by the performance of the FXS males included in the study,

especially given the relatively low IQs of the FXS males, the analyses were re-run on just the female

participants. Whilst the significance levels of some group comparisons were reduced, the pattern of

the results remained the same (see Figure 2b). In more detail, the FXS females remained

significantly worse than both the CA-matched (p = 0.013) and MA-matched (p = 0.044) females in

their ability to recognize angry expressions. They were also significantly worse at recognizing

neutral expressions compared to MA-matched females (p = 0.032), with a trend seen when

compared to the CA-matched females (p = 0.059). The significant difference in recognizing fearful

expressions compared to CA-matched controls, however, disappeared (p = 0.096). Overall, these

results suggest that the FXS males were not driving the observed group differences, except perhaps

the ability to recognize fear.

Error analyses revealed that the FXS group labeled 71.0% of the angry expressions as

neutral and 29.0% as fearful; consistent with proportions seen in both control groups (CA-matched:

60.0% neutral and 40.0% fearful; MA-matched: 50.0% neutral and 50.0% fearful). However, the FXS

group's neutral expression errors were distributed as 50.0% angry, 30.0% happy and 20.0% fearful,

disproportionate to both control groups in which all the neutral errors were mislabeled as angry.

These apparent differences in the groups' response biases, particularly for neutral expressions,

suggest the need for a measure of emotion recognition sensitivity. As such, a *d-prime (d')* value was

derived for each emotion based on their proportion correct (see Hacker and Ratcliff's (1979) m-AFC

tables, as cited in MacMillan and Creelman 1991). In more detail, *d'* calculates an individual's ability

to distinguish the target (correct) emotional expression from non-target (incorrect) emotions, with

a larger *d'* reflecting greater sensitivity in differentiating the target emotion from other emotions.

Results were consistent with those observed for the mean percent correct data, with planned

comparisons revealing that the FXS group were significantly less sensitive, compared to both

control groups, at recognizing neutral (p's ≤ 0.022) and angry (p's ≤ 0.010) expressions. The FXS

group was also significantly less sensitive than the CA-matched controls only at recognizing fearful expressions ($p = 0.003$)[3].

Overall, providing partial support for our prediction, specific emotion recognition deficits were observed in the FXS group for angry and neutral expressions, but not fearful expressions, suggesting that visual scanning abnormalities might also be more apparent in this disorder for neutral and angry facial expressions.
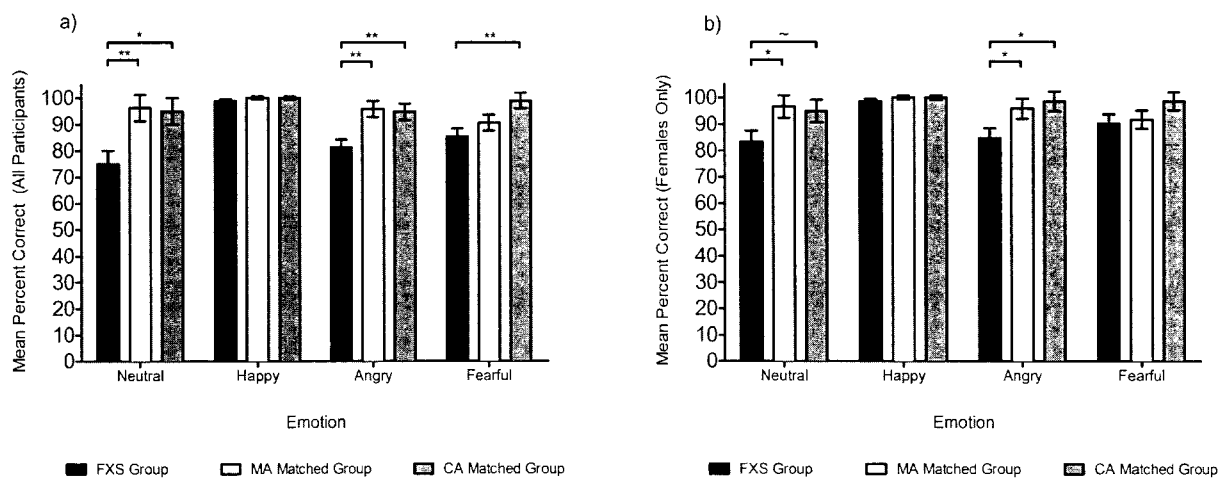

Figure 2. Emotion recognition (mean percent correct) for (a) All participants (b) Female participants only. Error bars represent standard error. ~ = p ≤ 0.1; * = p ≤ 0.05; ** = p ≤ 0.01

Visual Scan-paths

Do FXS individuals take longer to initially fixate on the eye region? A repeated measures ANOVA with Group as the between subject factor and Emotion as the within subjects factor on MTFF to the eye region showed a trend towards a significant main effect of Emotion [$F_{(3, 135)}$ = 2.44, $p = 0.067$, $\eta^2 = 0.05$], but no significant main effect of Group [$F_{(2, 45)}$ = 2.14, $p = 0.130$, $\eta^2 = 0.09$] or Group by Emotion interaction [$F_{(6, 135)}$ = 0.59, $p = 0.735$, $\eta^2 = 0.03$]. While these results suggest that the FXS group did not *initially avoid* the eye region compared to controls, inspection of

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[3] The analysis was conducted with males excluded and the pattern of results was similar. The only modification to results was that the difference between the FXS and CA-matched controls for sensitivity in recognizing neutral expressions now failed to reach significance ($p = 0.101$).

Table 2, which displays the means and standard errors for each emotion and group, suggest that the FXS group took longer overall compared to the CA-matched control group to initially fixate on the eye region. Post-hoc t-tests confirmed that this difference was significant (p = 0.040).

Do FXS individuals attend less to the eye region overall? A repeated measures ANOVA with Group as the between subject factor and Emotion as the within subjects factor on MDTP to the eye region revealed a significant main effect for both Group [F (2, 45) = 3.83, p = 0.029, η^2 = 0.15] and Emotion [F (3, 135) = 7.26, p < 0.001, η^2 = 0.14], but no Group by Emotion interaction [F (6, 135) = 0.75, p = 0.610, η^2 = 0.03]. As displayed in Figure 3, the CA-matched control group spent more time attending to the eye region of all emotional faces (M = 43.4%, SE = 4.0%) than both the FXS (M = 30.5%, SE = 4.0%, p = 0.027) and MA-matched control (M = 29.4%, SE = 4.0%, p = 0.017) groups. The main effect of Emotion was explained by significantly higher MDTP to the eye region of fearful expressions compared to all others emotions. These results suggested that the FXS differed from CA-matched controls, but not MA-matched controls in the time spent attending to the eye region of emotional faces.

Table 2

Mean *(standard error)* time to first fixation (MTFF) in milliseconds by Group and Emotion

	FXS Group	MA-matched Group	CA-matched Group	
Neutral	1913.46 *(335.80)*	1609.88 *(335.80)*	1002.33 *(335.80)*	**1508.56 *(193.87)***
Happy	2633.79 *(437.16)*	1813.96 *(437.16)*	1451.67 *(437.16)*	**1966.47 *(252.39)***
Angry	2109.25 *(284.33)*	1644.08 *(284.33)*	1062.75 *(284.33)*	**1605.36 *(164.16)***
Fearful	1773.08 *(401.07)*	1589.42 *(401.07)*	1291.29 *(401.07)*	**1551.26 *(231.56)***
	2107.40 *(309.68)*	**1664.33 *(309.68)***	**1202.01 *(309.68)***	

Significant difference between FXS group and relative control group at: * = $p \leq 0.05$; ** = $p \leq 0.01$

Do individuals with FXS scan emotional faces in a qualitatively different manner? Previous research has shown a positive association between the number of 'runs' into salient AOIs and facial recognition accuracy in both typically developing and autistic individuals (Wilson et al. 2012). Wilson and colleagues suggested that this may reflect the manner in which individuals process faces, with more 'runs' into and out of an interest area representing a dynamic scanning approach. As such, the variable 'run count' was calculated where a 'run' was defined as entry into and exit out of a salient AOI, in a similar manner to Wilson et al. (2012). Salient AOIs were deemed to be: 'left eye', 'right eye', 'nose' and 'mouth' (i.e., 'brow' and 'other' AOIs were excluded). Both left eye and right eye were included independently in this analysis to better reflect dynamic scanning, consistent with Wilson et al. (2012). As the salience of a facial feature can differ depending on the emotion portrayed (e.g., the eyes are more informative for recognizing angry expressions, whereas the mouth is used to recognize happy expressions) dynamic scanning may differ depending on the emotional expression. As such, we ran a repeated measures ANOVA with Group as the between subject factor and Emotion as the within subjects factor on mean run count (MRC) to determine whether there was any significant group difference in dynamic scanning. Results revealed a significant main effect of Emotion [$F(3, 135) = 8.85$, $p < 0.001$, $\eta^2 = 0.16$], a trend towards a significant main effect of Group [$F(2, 45) = 2.78$, $p = 0.073$, $\eta^2 = 0.11$], but no Group by Emotion interaction [$F(6, 135) = 0.81$, $p = 0.565$, $\eta^2 = 0.04$][4]. The main effect of emotion was explained by more runs per trial being made for fearful expressions, compared to all other emotions. The trend towards a significant Group effect was explained by the CA-matched control group, on average, making more runs per trial (M = 12.19, SE = 0.79) than the MA-matched group (M = 9.84, SE = 0.79, $p = 0.040$), and the FXS group, albeit not significantly (M = 10.00, SE = 0.79, $p = 0.055$). There was no difference observed between the FXS and MA-matched groups ($p = 0.887$).

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[4] Descriptive analyses revealed one outlier in each of the CA and MA matched groups. Analyses were performed with both the outliers removed and retained. The pattern of results was the same for both analyses; as such these data points were retained in the analysis.
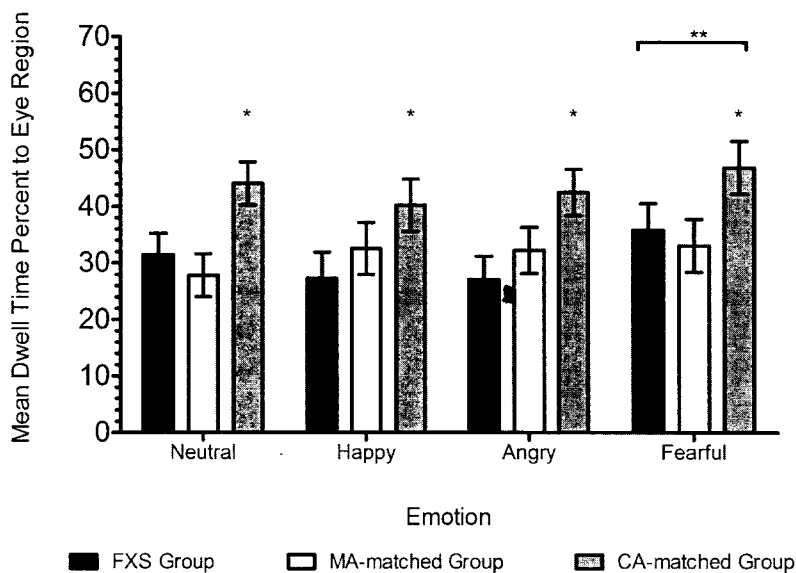
Figure 3. Mean dwell time percent to eye region by emotion. Error bars represent standard error. Lone asterisks represent main effect of group, asterisk and bar represents main effect of emotion. * = p ≤ 0.05

Levels of Social Anxiety, Schizotypy and Autistic Features

One-way ANOVAs for each measure (social anxiety z-score, schizotypal total score, autism total score) were conducted to investigate group differences. Table 3 displays the mean scores for the self- and parent-report measures and notes significant group differences. Results revealed significant main effects of Group for: total self-reported schizotypal features [$F_{(2, 44)} = 8.48$, $p = 0.001$] and total number of autistic features reported by parents [$F_{(2, 45)} = 6.37$, $p = 0.004$]. There was also a non-significant trend for self-reported social anxiety symptoms, with the FXS group endorsing higher levels of social anxiety symptoms than controls [$F_{(2, 45)} = 2.95$, $p = 0.064$]. Not unexpectedly, the FXS group was rated higher on all measures compared to both control groups.

Of the FXS group, 53.8% endorsed social anxiety symptoms above cut-off scores. Interestingly, the control groups also had a larger than expected proportion of individuals endorsing high levels of social anxiety, with 33.3% of the CA- and 12.5% of the MA-matched controls above cut-off. Chi-square analysis revealed a trend towards a difference between the groups [$\chi^2 (2, N = 44) = 5.67$, $p = 0.059$], with the FXS group having marginally more individuals scoring above cut-off

100

than the control groups. In terms of autistic features, one individual with FXS met the ABC cut-off indicative of autism (this individual had previously been formally diagnosed with autism); however, no controls were close to the cut-off score.

Table 3

Mean scores for self- and parent-report behavioral indices

	FXS Group			MA-matched Group			CA-matched Group		
	Mean *(SD)*	Range	n	Mean *(SD)*	Range	n	Mean *(SD)*	Range	n
SPAI(-C) [a]	0.3 *(0.7)*	-0.7 – 1.1	13	0.0 *(0.5)*	-0.9 – 0.9[*]	16	-0.1 *(0.3)*	-0.6 – 0.3[*]	15
STA [b]	23.5 *(9.2)*	6.0 – 42.0	14	16.8 *(8.2)*	1.0 – 35.0[*]	16	11.5 *(5.8)*	4.0 – 26.0[**]	15
ABC [c]	14.8 *(18.0)*	0.0 – 69.0	15	2.0 *(3.0)*	0.0 – 11.0[**]	16	3.3 *(5.6)*	0.0 – 20.0[**]	15

[a] SPAI(-C) = Social Phobia and Anxiety Inventory (Adult and Child versions) z-score (mean = 0.0, SD = 1.0). Missing data: three FXS males and one male CA-matched control.
[b] STA = Schizotypy Traits Questionnaire (max total score = 64). Missing data: two FXS males and one male CA-matched control.
[c] ABC = Autism Behavior Checklist (total score > 64 indicative of autism; max total score = 158). Missing data: one parent of a FXS female and one male CA-matched control's informant.
Significant difference between FXS group and relative control group at: * = $p \leq 0.05$; ** = $p \leq 0.01$

Correlations

Spearman correlational analyses were conducted to investigate the relationships between emotion recognition ability, scan-path parameters and behavioral indices. For emotion recognition ability, as the pattern of correlations for *d'* were the same as those observed for mean percent correct, as such only mean percent correct is reported. Some caution is required when interpreting these results due to the relatively small sample size (n = 16) and the number of correlations.

Firstly, correlations between MA, CA and emotion recognition (mean percent correct) and specific visual scan-path parameters (MTTF, MDTP to eye region, and MRC) were conducted. For the FXS group, results indicated a significant negative correlation between CA and emotion recognition ability of neutral expressions (r = -0.563, p = 0.023). This finding most likely reflected a sampling artifact with the two oldest FXS participants being males, and this significant correlation disappeared when only FXS females were included (r = -0.407, p = 0.189). When only FXS females

were included, a significant relationship between CA and ability to recognize angry expressions emerged (r = -0.652, *p* = 0.022); suggesting that the ability to accurately recognize angry expressions decreases with CA in FXS females. There was no significant correlation between IQ and emotion recognition ability or any visual scan-path parameters in the FXS females. With respect to controls, no significant correlations were observed for either control group overall or, as expected, when only female controls were included.

Next, the relationships between emotion recognition accuracy (mean percent correct) and visual scan-path parameters (MTTF and MDTP to eye region, and MRC) were explored in the FXS group. As there was very little variability in emotion recognition performance in the MA- and CA-matched control groups, these relationships were only explored in the FXS group. Significant correlations are displayed in Table 4 for both the FXS group as a whole, and separately for the FXS females. Consistent with our prediction, results indicated that better overall emotion recognition accuracy was significantly associated with quicker MTFF to the eye region, longer MDTP to the eye region, and more MRC per trial for the whole FXS cohort, and these moderate correlations remained when only FXS females were included, although the significance values were reduced.

Table 4

Significant correlations between emotion recognition and visual scan-path parameters for the whole FXS cohort and FXS females only

| | Emotion Recognition (% Correct) | | | | |
	Total	Neutral	Happy	Angry	Fearful
MTFF to Eye Region	**-0.610***	-0.488~	-0.028	-0.326	**-0.542***
	-0.536~	*-0.490~*	*-0.131*	*-0.155*	*-0.257*
MDTP to Eye Region	**0.548***	0.362	0.028	0.460	0.479~
	0.630*	*0.532~*	*0.131*	*0.332*	*0.362*
MRC per trial	**0.644****	0.532~	0.196	**0.611***	**0.622****
	0.511~	*0.162*	*0.306*	*0.388*	*0.428*

~ = p ≤ 0.1; * = p ≤ 0.05; ** = p ≤ 0.01

Lastly, correlational analyses were conducted to investigate the relationships between social anxiety, autism and schizotypy symptoms, emotion recognition ability and the same visual scan-path parameters. Results provided some support for our hypothesis that higher rating of social anxiety, schizotypy and autism would be associated with both poorer emotion recognition and more aberrant visual scan-paths. Significant correlations were found between social anxiety scores and overall MDTP to the eye region (r = 0.599, p = 0.031), and more specifically for angry expressions (r = 0.626, p = 0.022). Unexpectedly, these results suggest that increased levels of self-reported social anxiety were also significantly and *positively* associated with increased time spent attending to the eye region.

Discussion

The main aim of the current study was to investigate emotion recognition and visual scanning of emotional facial expressions (neutral, happy, angry and fearful) in individuals with FXS compared to typically developing CA- and MA-matched controls.

Providing partial support for our first hypotheses, the FXS group displayed specific emotion recognition deficits for angry and neutral expressions, compared to CA- and MA-matched control groups (prediction 1a); however no negative bias was observed (prediction 1b). Despite emotion recognition deficits being evident, contrary to our second hypothesis, no abnormalities in visual scan-paths were observed in the FXS cohort (predictions 2a-c). In fact, findings revealed that while individuals with FXS displayed reduced attention to the eyes and scanned emotional faces significantly differently compared to CA-matched controls, these individuals scanned emotional faces similarly to MA-matched controls. This finding suggests a developmental delay rather than a specific deficit scanning emotional facial expressions in the FXS individuals.

The third aim of this study was to explore the relationship between emotion recognition abilities and visual scan-paths; with the findings providing partial support for our hypothesis in that visual scan-path parameters were associated with overall emotion recognition performance. The final objective was to examine relations between emotion recognition, visual scan-paths and levels

of social anxiety, schizotypy and autism. Two main associations were observed; specifically, social anxiety symptoms were positively associated with time spent attending to the eye region, particularly for angry facial expressions.

Emotion Recognition in FXS

Neutral facial expressions. Our finding of a deficit in recognizing neutral expressions in FXS is consistent with previous research investigating both FXS premutation carriers (Cornish et al. 2005) and those with the FXS full mutation (Hagan et al. 2008). Taken together these findings provide emerging evidence that individuals along the entire FXS spectrum have difficulties processing neutral facial expressions (Cornish et al. 2005; Hagan et al. 2008; Hessl et al. 2007), albeit potentially to a lesser degree in FXS females. While a deficit for neutral expressions was apparent, the pattern of errors did not support our prediction that FXS individuals would display a negative bias for ambiguous expressions. Rather, errors were generalized across all emotional expressions; providing additional support for neutral expressions being more difficult to recognize for the FXS group, compared to controls (see Kuusikko et al. 2009). Alternatively, this lack of observed negative bias may reflect their difficulties recognizing angry facial expressions. This angry specific deficit may in fact reduce the likelihood of spontaneously misidentifying neutral facial expressions as negative (angry) ones.

Angry facial expressions. The specific deficit in recognizing angry expressions in our FXS cohort is of interest. While such a result has not been reported previously in FXS, it is consistent with previous research into schizophrenia (David and Cutting 1990), schizotypy (Mikhailova et al. 1996; Poreh et al. 1994), and to a lesser extent autism (Pelphrey et al. 2002). More importantly, the suggestion of a specific deficit in recognizing angry expressions is also consistent with emerging evidence of amygdala dysfunction within FXS (e.g., Hessl et al. 2007; 2011; Suvrathan and Chattarji 2011). Structural and functional amygdala abnormalities have been reported in animal models of FXS (Suvrathan et al. 2010; Suvrathan and Chattarji 2011). Such abnormalities have also been reported in humans with the FXS premutation (Hessl et al. 2007; 2011); as well as toddlers (Hazlett et al. 2009), older children and adolescents (Gothelf et al. 2008; Watson et al. 2008) with the FXS

full mutation. While the structural deficits of reduced amygdala volume have been reported consistently (e.g., Gothelf et al. 2008; Hazlett et al. 2009; Hessl et al. 2011), the evidence for related functional abnormalities has been more equivocal.

For example, Watson and colleagues (2008) reported *increased* amygdala response to direct eye gaze in a sample of FXS adolescent boys, whereas Hessl and colleagues (2011) have consistently reported *reduced* amygdala activation in premutation carriers when viewing threatening (fearful and angry) faces. As Hessl et al. (2011) concede, these differences may relate to the complex interplay between the underlying molecular-genetic mechanisms of the disorder, differing developmental level between individuals with the premutation and the full-mutation, or the tasks themselves (e.g. direction of eye gaze in face images). These differences may also relate to the fact that higher levels of social anxiety are typically observed in individuals with the FXS full mutation, compared to the premutation (e.g., Roberts et al., 2008). Individuals with social anxiety disorder have consistently been reported to display increased amygdala response to both neutral (Birbaumer et al. 1998) and negative emotional faces (Stein et al. 2002). As such, those individuals with the FXS full mutation may in fact have increased amygdala activation due to their higher levels of social anxiety; something neither Hessl et al. (2011) nor Watson et al. (2008) measured in their FXS cohorts.

While there is clearly more research to be done, these FXS neuroimaging studies nevertheless highlight the importance of the amygdala in the processing of facial expressions within the FXS population, and of the relationship between fragile X mental retardation protein (FMRP) levels and amygdala dysfunction (see Hessl et al. 2011). Our finding of a deficit for negative emotion processing provides additional, albeit indirect, support for amygdala dysfunction within the FXS population.

Interestingly, this same pattern of a specific deficit for angry expressions was found in previous work with WS, which employed the same paradigm (Porter et al. 2010). While most studies have not reported an anger-specific emotion recognition deficit in WS (e.g., Porter et al. 2007; Levy et al. 2011), there is emerging evidence that individuals with WS: do not process angry

faces in the same manner as MA-matched controls; display hypo-arousal, when presented with angry faces (Plesa Skwerer et al. 2009), as well as reduced detection (Santos et al. 2010); and have greater difficulty in generating angry expressions (Afshar and Porter, in prep.). Using the same stimuli as Porter et al. and for both the visual scanning and emotion recognition parts of the experiment allowed us to compare reported accuracy rates, which were similar for all control groups (> 90% correct). This, together with the fact that Ekman's widely used and well-standardized facial stimuli were used (Ekman and Friesen 2003) suggests that it is unlikely that these anger-specific deficits are derived from problematic stimuli; although this cannot be ruled out at this stage. Rather, these findings suggest that a deficit in recognizing angry facial expressions may, in fact, be a clinical phenomenon of both FXS and WS: an idea that is supported by emerging evidence of amygdala dysfunction in both FXS and WS (e.g., Haas et al. 2009; Hessl et al. 2007; 2011; Meyer-Lindenberg et al. 2005; Suvrathan and Chattarji 2011).

Alternatively, there may only be differences in the ways in which atypical or subtle facial expressions are either processed or interpreted by FXS individuals, and potentially those with WS. For example, 50% of the identities used as our stimuli had an angry expression which involved a closed mouth. Closed mouth angry expressions may be less typical and more subtle representations of the emotion, thus making it more difficult to recognize compared to other emotions such as happiness (Calvo and Marrero 2009). This is partially supported by findings from a study investigating emotion recognition and social approach behavior in FXS, with results indicating that FXS individuals were marginally worse than MA-matched controls at recognizing high intensity anger expressed by children (Shaw et al, in prep.). Future research should further explore the possibility of emotion specific deficits for angry expressions in FXS. Specifically investigating differences in emotion recognition ability for typical versus either atypical or subtle representations of an expression may provide additional insight into the nature of any deficits observed. Moreover, measuring reaction times for the emotion recognition task may highlight subtle difficulties in emotion recognition.

Visual Scan-paths in FXS

Consistent with previous studies (e.g., Dalton et al. 2008; Farzin et al. 2009; 2011; Holsen et al. 2008), our findings revealed aberrant scanning and reduced attention to the eyes in our FXS group, compared to a CA-matched control group. However, to the best of our knowledge, the current study is the first to explore visual scanning of faces in FXS, compared to a MA-matched control group. Contrary to our prediction, we found no differences between the FXS and MA-matched control groups in terms of the amount of time spent looking at the eye region, or the manner in which emotional faces were visually processed. This finding suggests that there is no obvious abnormality in the visual processing of emotional facial expressions in FXS. Rather, the abnormalities observed in previous studies of FXS can perhaps be best explained as reflecting developmental delay, rather than a specific deficit in emotional face processing per se.

The finding that visual scan-paths in FXS are determined by developmental level is consistent with those previous FXS studies, which have reported no specific face processing deficits in the disorder (e.g., Wishart et al. 2007). This suggestion of developmentally appropriate face scanning may also explain why there has been a lack of consensus regarding emotion recognition difficulties in FXS when picture-to-picture matching paradigms are used (Mazzocco et al. 1994; Simon and Finucane 1996; Turk and Cornish 1998; Wishart et al. 2007). As basic face scanning seems to be consistent with developmental age in FXS, we need to look at other explanations for the emotion recognition deficits that are observed in the disorder.

Emotion Recognition, Face Scan-paths and the FXS Phenotype

Chronological age. The observed significant negative relationship between CA and emotion recognition ability, particularly for neutral expressions, suggests that emotion recognition performance decreases with age in the FXS cohort as a whole. This is inconsistent with both previous FXS research (Turk and Cornish 1998) and with the pattern observed in typically developing individuals (Thomas et al. 2007). This correlation disappeared, however, after removing the FXS males from the analysis, suggesting the greater impairments observed in FXS males was driving this effect.

Face scan-paths. Dynamic scanning of emotional faces, as indexed by the amount of fixation movement around the face (i.e., the number of times a FXS individual looks at and then away from salient internal features of a face), was significantly associated with better overall emotion recognition ability in the FXS group. This finding is not only consistent with previous research into visual scanning of faces in typically developing adults (Calder and Jansen 2005), but also with research of visual face scanning in individuals with autism. Specifically, research has shown that more 'strategic' (Pelphrey et al. 2002) and 'dynamic' scanning (Wilson et al. 2012) in autism is associated with better face processing. Wilson and colleagues reported this correlation in not only autistic individuals, but also typically developing children. In the current study, this significant association was present for all negative expressions (angry and fearful), but not neutral or happy facial expressions. The latter is not surprising as happy is the easiest emotion to recognize (Palermo and Coltheart 2004), and can be identified primarily from the mouth (Ekman and Friesen 2003). In contrast, both fearful and angry facial expressions require more integration of information from all internal features, and thus require more dynamic processing for accurate emotion recognition (Rump et al. 2009).

However, our index of dynamic scanning was not the only visual scan-path parameter to dictate whether emotion recognition was accurate in our FXS group. The current study also found that both earlier initial fixation to, and longer viewing of, the eye region was associated with better overall emotion recognition in the FXS group as a whole, especially for fearful expressions. Moderate, albeit non-significant, correlations were also seen between initial fixation to, and longer viewing of, the eye region of neutral expressions, as well as recognition of this expression. These findings suggest that attending to the eye region does play an important role in accurately recognizing fearful, as well as potentially neutral, facial expressions in FXS. Importantly, these moderate correlations remained when only FXS females were included, although the significance values were reduced.

FXS Phenotype. Consistent with both Farzin et al. (2009; 2011) and Dalton et al. (2008), we did not find significant correlations between autistic features and visual scan-path parameters in

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our FXS groups. While these previous studies did not directly investigate the relationship between autistic features and emotion recognition ability, in the current study, we found no significant relationships between autism symptoms and ability to recognize any emotion.

In contrast to what was predicted, higher levels of self-reported social anxiety were significantly associated with *increased* time spent attending to the eye region of emotional faces. This result is inconsistent with previous research, which has shown significant avoidance of facial features, particularly the eyes, in socially anxious (non-FXS) individuals compared to controls (Horley et al. 2003; 2004). This unexpected finding may relate to our FXS cohort's lower than expected levels of self-reported social anxiety in that the FXS group were only marginally higher than the control groups on the SPAI(C). Using a self-report measure of social anxiety with intellectually impaired individuals may also have led to inaccurate reporting of internal anxiety states; as the participants may not have had appropriate insight into the specific symptoms they experience. The use of a parental-report measure of social anxiety would be beneficial to corroborate self-reported levels of anxiety and would be beneficial to include in future research.

Medication use should also be considered when interpreting the findings. Both the lower levels of self-reported social anxiety and the positive correlation with time spent viewing the eye region may be due to anti-anxiety medication use. While medication use was not specifically recorded for the current study, interview notes suggest that approximately half of our sample were on anti-anxiety medication at the time of testing; consistent with levels reported elsewhere in the literature (Berry-Kravis and Potanos 2004). If these FXS individuals have relatively well controlled anxiety, they may be displaying the hypervigilance that is characteristic of social anxiety without the avoidance. Specifically, they may have attended to and away from the eye region more often than controls leading to more time fixating on the eye region overall. While there was no significant relationship between mean run count and social anxiety symptoms, which may have provided additional support for this explanation, the mean run count variable includes all salient internal features (eyes, nose, and mouth) and thus does not single out the eye region. In future research, it

would be interesting to investigate social anxiety severity, medication use, and eye gaze avoidance in FXS individuals to tease apart this relationship further.

Limitations and Future Research

In addition to those limitations already noted above (e.g. the absence of some parent report measures), differences in methodology and other limitations need also to be considered when interpreting the current findings. There are noted methodological differences between the current study and previous studies investigating visual scan-paths to emotional faces in FXS (Dalton et al. 2008; Farzin et al. 2009; 2011; Holsen et al. 2008). These differences include: the stimuli and emotional expressions used, as well as presentation times and task demands. All previous studies used a presentation time of 3,000ms. Tasks employed previously also ranged from passive viewing (Farzin et al. 2009; 2011) to emotional face judgments (Dalton et al. 2008) paradigms, with the latter being shown to alter visual scanning (Hayhoe and Ballard 2005). Importantly, we don't believe that any one, or all, of these methodological differences can fully explain the current findings. Firstly, all studies used face stimuli sets which are well standardized (see Palermo and Coltheart 2004). Secondly, while one could argue that our longer presentation of stimuli may have masked any subtle avoidance of the eye regions (with the FXS taking longer to attend the eye region rather than avoid it altogether), we found no difference between the groups in time to first fixate on the eye region and the mean for each group was well within 3,000ms (means ranged from 1,200-2,100ms). Future studies would benefit from directly investigating differences in emotional face processing as a function of presentation time, particularly in light of the dynamic nature of facial expressions in everyday life (Rump et al. 2009).

While the sample size in the current study was relatively small with respect to FXS research in general, it is similar to other studies investigating physiological indices within the population (e.g., Dalton et al. 2008; Farzin et al. 2009; 2011). It is important though to take into account the heterogeneity within the FXS population and the influence that factors such as gender, CGG repeats, FMRP levels and activation ratios may have on individuals' cognitive and behavioral functioning (see Hagerman 2002 for a review). This is particularly relevant with respect to

replicating and generalizing the current study's findings, as our sample heavily consisted of females with FXS. While Cornish and colleagues (2005) found no significant correlation between CGG repeats and emotion recognition abilities in their sample of FXS premutation carriers, further investigations into molecular correlations in the FXS full mutation is warranted. We concede that it is a limitation of the current study that detailed molecular genetic information could not be obtained, and we encourage this research in the future. For example, FMRP expression has been shown to be a prognostic indicator in males with the FXS full mutation (Tassone et al. 1999) and is associated with amygdala dysfunction in FXS (Hessl et al. 2011); thus focusing on FMRP levels may provide insight into the relationship between molecular markers and emotion processing skills. To empirically investigate the influence of these factors, future studies should focus on larger sample sizes and including different subgroups of FXS individuals (varying, e.g., gender, FXS status, molecular genetics, comorbid diagnoses) to provide an opportunity to subgroup FXS individuals, based not only on these important variables, but also on their emotion recognition and visual scan-path characteristics.

Future research would also benefit from concurrent emotion recognition, visual scan-path recording and neuroimaging recording to further explore the relationships between emotion recognition abilities, visual scan-path patterns and neural activation. There have been limited studies investigating visual scan-paths and neurophysiological measures in FXS (Dalton et al. 2008; Holsen et al. 2008); with none directly measuring emotion recognition abilities. Rather they have relied on dichotomous facial-emotion (emotion present or not; Dalton et al. 2008) or gender (male face or female face; Holsen et al. 2008) discrimination tasks, which do not allow explicit emotion recognition to be assessed. There is evidence that neural pathways are disrupted in FXS during explicit emotion recognition, at least for neutral facial expressions (Hagan et al. 2008). Thus, our focus should turn to methodologies which allow for direct comparison across emotions, whilst measuring brain activation in order to investigate potential brain abnormalities which may underlie the specific negative-ambiguous recognition problems that are emerging in the FXS literature (Cornish et al. 2005; Hagan et al. 2008; Hessl et al. 2007). Whilst it is a limitation of the current

study that we did not measure emotion recognition abilities and visual scanning concurrently, we believe that including both tasks is a strength of this research, and that future research might include concurrent measurement of explicit and implicit emotion recognition abilities.

Elucidating the locus of these emotion recognition deficits is potentially the most important future direction for this area of research. This future work will not only provide insight into the nature of these deficits, but will inform potential remediation and treatment programs. There are a number of different ways of investigating this area without having to rely solely on neuroimaging, which is notoriously difficult to conduct with the FXS population. Specifically, different socio-emotional paradigms, including both explicit and implicit tasks, could be employed to tap different aspects of how individuals extract emotional information from faces. Research into patients with damage to the orbitofrontal cortex (OFC) have been reported to show intact explicit emotion recognition skills, alongside an impaired ability to successfully use facial expressions to guide approachability judgments (Willis et al. 2010); suggesting that judging the approachability of emotional faces may dissociate functionally from the ability to explicitly recognize the same emotions. As such, different brain regions may play different specific roles in interpreting information from emotional faces. Of particular interest is that the OFC has been reported to play a role in processing negative facial expressions (Willis et al. 2010); a deficit the current study observed in FXS.

Similar dissociations of explicit (emotion recognition) and implicit (social judgment) processing have also been observed in other neurodevelopmental disorders such as autism (Adolphs et al. 2001) and WS (Porter et al. 2007). Moreover, neural abnormalities in the frontal lobes of FXS individuals have also been noted (see Lightbody and Reiss 2009 for a review), including disruption of the OFC (Tamm et al. 2002). Imaging studies that report amygdala dysfunction in FXS also exist (Gothelf et al. 2008; Hazlett et al. 2009; Hessl et al. 2007). As such, investigating approachability judgments in FXS may provide a better understanding of whether we can dissociate between these individuals' explicit and implicit emotion processing skills, and help to identify what neural disruptions, if any, can best explain the pattern of results.

General Conclusion

The current study provides empirical evidence that individuals with FXS display specific emotion recognition deficits. These deficits are seen for negative (anger) and ambiguous (neutral) emotional expressions, with FXS participants performing significantly worse than both CA- and MA-matched controls. However, these emotion recognition deficits are unlikely to be due to visual scanning abnormalities, as the manner in which the FXS individuals visually scanned the emotional facial expressions was consistent with the scanning of MA-matched controls. Further elucidation of the underlying causes of the emotion recognition deficits in FXS could better inform remediation programs and social skills training, with a particular view to early intervention.

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Author Notes

Chapter 5 – Hyperarousal in Fragile X Syndrome Females: Generalised or Social-specific? A Skin Conductance Study

Hyperarousal in Fragile X Syndrome Females: Generalised or Social-specific? 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 hypothesized that the FXS social phenotype is secondary to a generalised hyperarousal 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 FXS females, 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, FXS females displayed hyperarousal only when viewing the more socially salient stimuli (emotional faces), compared to CA-matched controls, but not MA-matched controls. Moreover, FXS females also displayed atypical emotion recognition abilities and subjective ratings of their own emotional states. These findings suggest that any hyperarousal observed in FXS may be more social-specific rather than generalised.

Hyperarousal in Fragile X Syndrome Females: Generalised or Social-specific? A Skin Conductance Study

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, Reiss, & Abrams, 1993; Hagerman, 2002; Lachiewicz, 1992; Mazzocco, Kates, Baumgardner, Freund, & Reiss, 1997) to a similar, yet more varied degree than FXS males. In fact, although FXS females typically display milder levels of intellectual impairment than their male counterparts, significant socio-emotional difficulties still remain apparent (see Keysor & 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 FXS females presenting with notable ADHD symptoms despite their not meeting criteria for a formal diagnosis (Keysor & Mazzocco, 2002). The presence of ADHD symptoms in FXS will likely impact on daily functioning, with several studies reporting that children and adolescents with ADHD display significant difficulties creating and maintaining interpersonal relationships with both their peers and adults (see for example, Charman, Carroll, & Sturge, 2001; DuPaul, McGoey, Eckert, & VanBrakle, 2001).

In addition to the presence of ADHD symptoms in FXS females, these individuals display significantly more autistic behaviours than gender- and chronological age- (CA-) matched controls (Mazzocco, et al., 1997; Reiss & Freund, 1992). Such autistic behaviours include stereotypies, communication difficulties and deficits in social interactions (particularly with peers). In a recent Australian study, the percentage of FXS females who met diagnostic criteria for autism was approximately 10%. Although this was a lower prevalence than the 18% of FXS males who met diagnostic criteria for autism within the same study (Clifford et al., 2007), it remains well above the baseline prevalence rate of 9.6–40.8 per 10,000 in the typically developing population (Williams, MacDermott, Ridley, Glasson, & Wray, 2008).

Anecdotal reports suggest that social anxiety is one of the most debilitating features experienced by females with FXS. This social anxiety presents from an early age, with excessive shyness and social avoidance observed in FXS females from early childhood (Freund, et al., 1993;

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Sobesky, Hull, & Hagerman, 1994; Sobesky, Pennington, Porter, Hull, & Hagerman, 1994). Not surprisingly then, research has shown that social anxiety disorder (Franke, Barbe, Leboyer, & Maier, 1996; Tsiouris & Brown, 2004) and avoidant personality disorder (Freund, et al., 1993) are reported more frequently than other anxiety disorders (e.g., generalised anxiety disorder) in females with FXS (e.g., see Freund, et al., 1993). Abnormal social behaviours, which are consistent with schizotypal personality disorder, are also commonly observed in FXS females. Such abnormal behaviours include social oddness, avoidance of direct eye contact, and difficulty building rapport (Sobesky, Hull, et al., 1994).

The fact that social anxiety, schizotypal traits and autistic behaviours are commonly reported in FXS females (Hagerman, 2002) suggests a need to investigate the socio-emotional processing skills of FXS individuals in more detail. This is particularly so because individuals with social anxiety (e.g., Simonian, Beidel, Turner, Berkes, & Long, 2001), schizotypal personality disorder (e.g., Mikhailova, Vladimirova, Iznak, Tsusulkovskaya, & Sushko, 1996) and schizophrenia (see Edwards, Jackson, & Pattison, 2002), as well as autism (Celani, Battacchi, & Arcidiacono, 1999; Pelphrey et al., 2002), are known to display emotion recognition problems. While early research into the emotion recognition abilities of FXS individuals has reported that these abilities are intact or, when impaired, explained by lower IQ in FXS (e.g., Mazzocco, Pennington, & Hagerman, 1994; Turk & Cornish, 1998; Wishart, Cebula, Willis, & Pitcairn, 2007), more recent studies have suggested that domain-specific emotion recognition difficulties may be present in FXS (Cornish et al., 2005; Hagan, Hoeft, Mackey, Mobbs, & Reiss, 2008; Shaw & Porter, 2012). While methodological differences between the earlier research and these later studies may explain the disparate findings, it is clear that more research is required to better elucidate the emotion recognition abilities in FXS.

With the field of socio-emotional neuroscience rapidly expanding, and the increased use of psychophysiological measures of social abilities, such as electrodermal activity (EDA), heart rate and pupillometry, researchers are beginning to go beyond explicit measures (e.g., facial affect recognition) to investigate more implicit aspects of social and emotional processing in

developmental and acquired disorders. Specifically, psychophysiological methodologies allow investigation of concurrent underlying implicit processes when explicit responses to socio-emotional tasks are demonstrably abnormal. More importantly, perhaps, these measures also allow researchers to investigate potential abnormalities even when overt behavioural responses on explicit socio-emotional tasks appear to be relatively intact. As Karmiloff-Smith (1998) asserted, it is important to distinguish between the explicit performance on tasks and the mental processes underlying that performance, which may be abnormal, even when overt measures reveal no demonstrable impairment. This is particularly pertinent for FXS as the findings to date from explicit emotion recognition studies are equivocal.

Moreover, with the aforementioned reports of heightened levels of hyperactivity and hyper-reactivity (Hagerman, 2002; Mazzocco, 2000; Miller et al., 1999), autistic tendencies (Clifford, et al., 2007) and social anxiety (Tsiouris & Brown, 2004) in FXS, researchers have hypothesized 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 generalized hyperarousal that leads to an avoidance of, or withdrawal from, social stimuli (Cohen, 1995; Cornish, Sudhalter, & Turk, 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, as discussed in further detail in the following subsections.

Psychophysiology and Arousal

Electrodermal activity (EDA) is a widely used psychophysiological measure that relates to the change in electrical conductance of the skin surface and incorporates both slow alterations in base skin conductance levels (SCLs) as well as more rapid event-related changes referred to as skin conductance responses (SCRs; Critchley, 2002; Dawson, Schell, & Filion, 2007). EDA is considered to be one of the most sensitive indices of autonomic nervous system (ANS) activity (Dawson, et al., 2007); and more specifically, changes in sympathetic arousal associated with attention, emotion and cognition (see Critchley, 2002 for a review). SCRs can be elicited by

various stimuli, including those that are novel (e.g., Smith, Davidson, Smith, Goldstein, & Perlstein, 1989), familiar (e.g., famous/familiar faces; Heard & Nash, 2009), and threatening (e.g., angry faces; Lang, Greenwald, Bradley, & Hamm, 1993). In general, though, SCRs are elicited by stimuli which are considered to be subjectively salient for the individual (Critchley, 2002), and are therefore considered to be sensitive to the general level of *arousal* elicited by the stimulus rather than the particular *valence* of the stimulus (Lang, et al., 1993). For example, findings from a recent meta-review of 134 articles investigating emotion and ANS arousal revealed that both positive and negative emotional images elicited increased SCRs (Kreibig, 2010). As the size of an individual's SCR is contingent upon how salient an individual considers the eliciting stimulus to be, one might speculate that individuals with particular developmental and acquired conditions, which are thought to be associated with social hyperarousal, may display greater SCRs to socially salient stimuli.

In accord with this hypothesis, individuals with social anxiety, who show pre-attentive vigilance and selective attention to threatening faces (Mogg & Bradley, 2002; Mogg, Philippot, & Bradley, 2004) and increased limbic activation compared to controls during implicit and explicit processing of angry faces (Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004), also show increased SCRs to socially relevant information. For example, researchers have reported that individuals with high levels of social anxiety display increased autonomic arousal to facial stimuli (Dimberg, 1997; Dimberg & Christmanson, 1991), as well as during public speaking tasks (e.g., Heimberg, Hope, Dodge, & Becker, 1990; Hofmann, Newman, Ehlers, & Roth, 1995). However, individuals with social anxiety have also been shown to display larger SCRs and reduced habituation to non-social stimuli (e.g., intense tones; Lader, 1967; Roth, Ehlers, Taylor, Margraf, & Agras, 1990); suggesting that these individuals may suffer from generalised hyperarousal rather than hyperarousal specific to socially salient information.

Individuals with paranoid schizophrenia have also displayed significantly more frequent SCRs and larger SCRs when viewing fearful facial expressions (Williams et al., 2004), as well as reduced SCR habituation (Schiffer, Sigal, & Mintz, 1996) compared to typically developing

controls. While similar findings have been reported in children and adolescents with autism (e.g., Hirstein, Iversen, & Ramachandran, 2001; Kylliainen & Hietanen, 2006), heterogeneity within autism in this regard has also been noted. For example, Hirstein and colleagues (2001) reported that 30% of their autistic sample displayed significant *hypo*arousal rather than *hyper*arousal during a 35 minute social interaction task (Hirstein, et al., 2001, Exp. 2). Interestingly, these researchers also reported that, while an un-matched typically developing control group produced significantly larger SCRs to social stimuli (making eye contact with a familiar person) than non-social stimuli (looking at a paper cup), this difference was not observed in the autistic group (Hirstein, et al., 2001, Exp. 1). Additionally, Shalom and colleagues (2003; 2006) investigated SCRs to affective non-social stimuli (e.g., unpleasant, pleasant and neutral non-social images) in children with high-functioning autism compared to CA-matched typically developing controls. Their results showed that, while SCRs did not differ between the groups for pleasant, unpleasant or neutral non-social images, the groups did differ in their subjective ratings of pleasantness and interest (Shalom et al., 2006; 2003). According to these researchers, the findings suggested that individuals with autism display deficits in the perception and/or expression of conscious feelings, rather than abnormal autonomic responding, at least for non-social affective stimuli.

As individuals with FXS display significant social anxiety, as well as schizotypal and autistic tendencies, it is particularly relevant to explore autonomic arousal levels to different types of stimuli in these 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; Roth et al., 1990; Hirstein, et al., 2001). The relevant background to this question is reviewed in the following subsection.

Psychophysiology in Fragile X Syndrome

Early psychophysiological research in FXS focused 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 FXS males, one ADHD male and one male with Down syndrome (DS) were measured while the participants engaged in conversations with a

stranger. Results revealed that the two FXS males 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 and colleagues (1999) extended Belser and Sudhalter's (1995) work with FXS males 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. Using the same sensory challenge protocol, Hagerman and colleagues (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 and colleagues (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 FXS females were compared to females with Turner syndrome and a CA- and gender-matched control group. Results indicated that the FXS females 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, Mazzocco, McLeod, & Hoehn-Saric, 2002). Interestingly, heart rate studies have also reported similar findings of increased arousal at baseline in young males and females with FXS (Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009; Roberts, Boccia, Bailey, Hatton, & Skinner, 2001). For example, Hall and colleagues (2009) reported increased heart rate at baseline *and* during a social interaction task in their large sample of FXS males and females, compared to a gender-matched sibling control group (Hall, et al., 2009). This hyperactivity 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, Rivera, & Hessl, 2009; Farzin, Scaggs, Hervey, Berry-Kravis, & Hessl, 2011). In contrast to Hall and colleagues (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 hyperarousal 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 hyperarousal 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.

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 would be expected 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 amplitudes and increased SCR frequencies compared to both control groups, irrespective of the stimulus set. We also predicted that these differences between groups would be more marked for the direct-gaze faces compared to the affective scenes. Thus, we hypothesized that, while the FXS group would display generalised hyperarousal, this would be particularly heightened when the participants viewed more socially salient information.

Of secondary interest, 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. 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.

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[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%). Importantly, no affective images contained faces with direct-gaze.

Method

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.

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 and genetic testing confirmed the 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 FXS cohort fell in the mildly-to-moderately impaired range, which is consistent with the literature. Parents reported that, while no FXS participant was on stimulant medication at the time of the current study, 58.3% (n=7) were taking anti-anxiety or antidepressant medication.

Typically developing control participants. CA- and MA-matched controls were recruited through the Macquarie University Kids' Science Club and via advertisements distributed across the Macquarie University campus. Exclusion criteria were a history of learning difficulties, developmental delay, intellectual impairment, as well as behavioural, psychological, sensory or cognitive deficits or a history of neurological compromise. No control participants were on any prescription medication at the time of their participation in the study. IQ and MA for all control participants were confirmed by the WASI. Details regarding CA, MA and FSIQ for both control groups are reported in Table 1.

Independent sample t-tests indicated that the control groups were well matched to the FXS group, with no significant difference in MA between the FXS and MA-matched control group

[t (22) = -0.04 p = 0.971] and no significant difference in CA between the FXS and CA-matched control group [t (22) = 0.15, p = 0.885].

Table 1

CA, MA and FSIQ by group

	FXS Group			MA-matched controls			CA-matched controls		
	Mean	*(SD)*	Range	Mean	*(SD)*	Range	Mean	*(SD)*	Range
CA [a]	20.6	*(7.1)*	12.1–38.1	8.8 *(3.9)*		5.9–20.3**	20.2 *(6.9)*		12.1–36.3
MA [a]	9.0	*(4.2)*	6.1–21.1	9.1 *(3.9)*		5.9–20.3	20.2 *(6.9)*		12.1–36.3**
FSIQ [b]	65.4	*(15.6)*	52.0–96.0	108.0 *(8.8)*		94.0–126.0**	106.1 *(8.9)*		91.0–118.0**

[a] Mean CA and MA in years
[b] FSIQ = Standard Score (mean = 100, SD = 15)
Significant difference between FXS group and relative control group: * $p \leq 0.05$; ** $p \leq 0.01$

Experimental Stimuli

Affective scenes. This stimulus set comprised 65 colour images selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1999). The IAPS is a large set of static colour photos that has been widely used in psychophysiological research and has been characterised along the dimensions of arousal and valence (see Mikels et al., 2005). Images were chosen based on their ability to elicit five different emotional categories (i.e., happiness, sadness, fear, disgust or neutrality; see Mikels, et al., 2005). Anger was not included as an emotional category as it has been consistently shown that 'angry' images are rated unreliably (Lang, et al., 1993; Mikels, et al., 2005). Thirteen images for each of the five emotional categories were chosen based on both Mikels et al.'s (2005) findings and our own set criteria[2], and were then rated by two independent judges to confirm that the chosen images adequately evoked the intended emotion. Agreement was > 80% for each emotion. An additional four IAPS images were

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[2] Positive: valence > 7, arousal > 5; sadness: valence < 4, arousal > 5; fear: valence < 4, arousal > 5; disgust: valence < 4, arousal > 4; neutral: 4 > valence < 5, arousal < 3

chosen to elicit the aforementioned emotional categories (neutral excluded) as practice stimuli and were not included in the analyses.

Direct-gaze emotional faces. Stimuli for the set of emotional facial expressions were selected from the Karolinska Directed Emotional Faces (KDEF; Lundqvist, Flykt, & Öhman, 1998). The KDEF is a database of 490 standardized and colour images consisting of 70 individuals (35 female) displaying 7 different emotional expressions at five different angles (see Lundqvist, et al., 1998). The KDEF's frontal view images have been independently validated (Goeleven, De Raedt, Leyman, & Verschuere, 2008). For the current study, 10 identities (5 female) were chosen, each displaying an angry, disgusted, fearful, happy, sad and neutral expression with direct eye-gaze; for a total of 60 faces. Practice trials consisted of four faces (one each of: angry, fearful, happy, and neutral) of a different identity to those used for the experimental stimuli; again the practice stimuli were excluded from all analyses.

Procedure

Physiological recording. The procedures for physiological recording during viewing of both sets of stimuli were identical. Participants were seated in a darkened room in a comfortable chair and viewed the stimuli on a 16" Dell laptop monitor from a distance of 60 cm (with viewing distance controlled by seat position). The SCR system was zeroed prior to attaching the electrodes to the participant. The electrodes were attached for approximately two minutes before the onset of the practice stimuli in order for the participant to become accustomed to the equipment and process. The SCR system was then zeroed again immediately prior to presentation of the practice items to standardise the participant's baseline. Recording was then continuous throughout the presentation of the stimuli. For each set, participants first passively viewed the four practice trials (in a fixed order), followed by the experimental stimuli presented in a randomised order for 4,000ms. For each trial, a fixation cross was presented in the centre of the screen for 16,000ms, followed by an image which then disappeared from the screen, to be replaced once again by the fixation cross. Thus, the inter-stimulus interval was set at 16,000ms to allow for the SCR to return to baseline. Between the two image sets, participants were given a short break and the SCR

machine was re-calibrated. Each set of images took approximately 20 minutes and the two sets were presented in a counterbalanced order.

Behavioural responses. After SCR data collection was completed for both sets, the participants were asked to view the stimuli in each set once again. The two sets were presented in the same order as seen during the SCR recording with the items within each set being presented in a fixed pseudo-randomized order. On this second occasion, participants were asked to either rate the evoked emotion for the affective scenes or identify the emotional expressions of faces, as outlined below.

For the set of affective images, participants were first asked to judge the emotional response they felt towards each affective scene ("How does that picture make you feel?") with a forced choice response: 'happy', 'sad', 'scared', 'disgusted' or 'normal'. Participants were then asked to rate the intensity of their emotional response ("How much does it make you feel that way?") on a scale from 1 to 5, with the anchors of 1 = "a little bit" and 5 = "completely". The scale was explained in detail prior to the experiment, and each participant was given a written list of the emotional choices and a visual scale to aid with responding. The experimenter read the emotional choices aloud when required. Participants were given unlimited time to respond.

For the set of emotional faces with direct gaze, participants were requested to verbally label the emotional facial expression displayed in a forced choice paradigm. To ensure minimal load on working memory all participants were given a written list of each possible option ('happy', 'sad', 'angry', 'scared', 'disgusted' or 'normal'), and the experimenter also read the list aloud if required. Again, images remained on the screen until the participant responded.

Physiological Measures and Data Analysis

Acquisition, amplification, and filtering of the physiological signals were conducted using ADInstruments PowerLab computer-based modular instrument system with Chart 5.4 Software (ADInstruments Inc., Sydney, Australia). SCRs were recorded in microSiemens (µS) using standard dry metal bipolar finger electrodes (model MLT116F). Electrodes were placed on the volar surface of the medial phalanges of each participant's non-dominant index and middle finger. Each

participant was instructed to keep their hand as still as possible throughout the entire experiment. A constant current of 22 micro volts was applied at 75 Hz through the electrodes to measure skin conductance.

To control for individual differences in skin conductance and any abnormal movement, SCR peak amplitudes were quantified by subtracting the average baseline response across the 1,000ms prior to a stimulus onset from the maximum value (i.e., peak), which occurred between 1,000ms and 5,000ms post-the stimulus-onset. A valid SCR was defined as an increase in amplitude of at least 0.02μS during this 4,000ms period, which is consistent with previous physiological studies (e.g., Plesa Skwerer et al., 2009) and within the range recommended by Dawson and colleagues (2007). All trials with SCRs below 0.02μS (i.e., non-responses) were removed from the analysis. Data were also cleaned to remove all SCRs deemed to be movement artefact rather than valid SCRs. SCR frequency, defined as the percentage of trials with a valid SCR, was also calculated.

Results

Physiological Responses

Inspection of the SCR data revealed significant positive skew; as such a log transformation (Log[SCR+1]), as recommended by Venables and Christie (1980), was used initially. However, transformation of the data did not improve the distributions to a satisfactory level, thus non-parametric Kruskal-Wallis analysis of variance (ANOVA) tests were used to analyse the SCR frequency and peak amplitude raw data.

Affective scenes. As displayed in Table 2, the overall mean SCR frequency was consistent across all groups (χ^2 (2, N = 36) = 0.85, p = 0.665, η^2 = 0.02); that is, all groups responded with a valid SCR on approximately 50% of all trials. In contrast, the overall mean SCR peak amplitude appeared to be higher in the younger MA-matched control group compared to the FXS and CA-matched control groups, although this overall difference didn't reach significance (χ^2 (2, N = 36) = 5.70, p = 0.058, η^2 = 0.16). However, as the patterns of SCR peak amplitudes across the different affective categories appeared to differ between the groups, we investigated each affective

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category further. Results revealed significant differences between the groups for the affective

categories of: happy [χ^2 (2, N = 36) = 7.77, p = 0.021, η^2 = 0.22], fearful [χ^2 (2, N = 36) = 8.08, p =

0.018, η^2 = 0.23] and disgusting [χ^2 (2, N = 36) = 9.50, p = 0.009, η^2 = 0.27]; but not sad [χ^2 (2, N =

36) = 3.51, p = 0.172, η^2 = 0.10] or neutral [χ^2 (2, N = 36) = 3.70, p = 0.157, η^2 = 0.11].

Follow-up Mann-Whitney U-tests revealed that all these group differences were driven by

the younger MA-matched controls displaying significantly higher SCR peak amplitudes than the

CA-matched controls for happy (U = 29.0, p = 0.013), fearful (U = 37.0 p = 0.043) and disgusting (U

= 19.0, p = 0.002) images. The MA-matched controls also displayed significantly higher mean SCR

peak amplitudes compared to FXS individuals for the happy (U = 32.0, p = 0.021) and fearful (U =

29.0, p = 0.006) affective categories, but not for the scenes that evoked disgust (U = 29.0, p =

0.149). There was no significant difference in mean SCR peak amplitude between the FXS and CA-

matched groups for any affective category (p's > 0.05).

Table 2

*Mean (SD) SCR amplitude and frequency for each **affective scene** category by group*

	FXS		MA-matched controls		CA-matched controls	
	Amplitude	Frequency	Amplitude	Frequency	Amplitude	Frequency
Happy	0.64 *(0.60)*	0.54 *(0.16)*	1.16 *(0.58)*	0.55 *(0.15)*	0.57 *(0.41)*	0.51 *(0.15)*
Sad	0.83 *(0.79)*	0.50 *(0.11)*	0.75 *(0.42)*	0.53 *(0.21)*	0.54 *(0.58)*	0.46 *(0.23)*
Fearful	0.47 *(0.28)*	0.51 *(0.19)*	1.02 *(0.46)*	0.53 *(0.19)*	0.61 *(0.49)*	0.51 *(0.21)*
Disgusted	0.65 *(0.46)*	0.51 *(0.20)*	1.00 *(0.60)*	0.53 *(0.15)*	0.34 *(0.22)*	0.49 *(0.21)*
Neutral	0.63 *(0.55)*	0.57 *(0.14)*	0.95 *(0.49)*	0.53 *(0.21)*	0.68 *(0.55)*	0.44 *(0.19)*
Overall	**0.64 *(0.47)***	**0.53 *(0.10)***	**0.98 *(0.42)***	**0.53 *(0.13)***	**0.55 *(0.37)***	**0.48 *(0.15)***

To sum the results thus far, the MA-matched control participants, who were younger than

the other two groups, showed significantly higher SCR peak amplitudes to the affective (IAPS)

scenes, more so for happy, fearful and disgusting images than for sad and neutral images. This

pattern of results suggests that younger CA may explain the observed group differences. This is supported by correlational analyses, in which CA (collapsed across clinical and control groups) was significantly and negatively associated with overall SCR peak amplitudes (r_{sp} = -0.653, p < 0.001).

Direct-gaze emotional faces. The mean SCR peak amplitude and frequency data for all groups when viewing the direct-gaze emotional faces are displayed in Table 3. As found for the affective scenes, the three groups did not show a significant group difference with regards to their overall frequency of valid SCRs (χ^2 (2, N = 36) = 3.76, p = 0.153, η^2 = 0.10). In contrast, there was a significant group difference for the overall SCR peak amplitude (χ^2 (2, N = 36) = 14.43, p < 0.001, η^2 = 0.41), with the younger MA-matched control group showing the largest SCRs overall. Follow-up Mann-Whitney tests revealed that the overall mean SCRs of the MA-matched controls were significantly larger than those of the FXS individuals (U = 32.0, p = 0.020), whose overall mean SCRs were, in turn, significantly larger than those of the CA-matched controls (U= 34.0, p = 0.028).

Results were then analysed separately for each emotion and revealed a significant group differences in mean SCR peak amplitude across all emotional facial expressions: happy [χ^2 (2, N = 36) = 14.85, p = 0.001, η^2 = 0.42], sad [χ^2 (2, N = 36) = 14.39, p = 0.001, η^2 = 0.41], angry [χ^2 (2, N = 36) = 9.32, p = 0.009, η^2 = 0.27], fearful [χ^2 (2, N = 36) = 11.69, p = 0.003, η^2 = 0.33], disgusted [χ^2 (2, N = 36) = 12.36, p = 0.002, η^2 = 0.35], as well as neutral expressions [χ^2 (2, N = 36) = 12.06, p = 0.002, η^2 = 0.34]. Mann-Whitney U-tests were conducted to follow-up these significant group differences. Results revealed that the younger MA-matched control group displayed significantly higher SCR peak amplitudes than the CA-matched control group for each emotional facial expression (all $U's$ ≥ 10.0, all $p's$ ≤ 0.003), as well as significantly higher SCR peak amplitudes than the FXS group for happy (U = 25.50, p = 0.007), sad (U = 28.0, p = 0.011) and fearful (U = 34.0, p = 0.028) facial expressions. Results also revealed that the FXS group produced significantly larger mean SCR peak amplitudes compared to the CA-matched control group for the disgusted facial expressions (U = 22.0, p = 0.003). No other comparisons between the FXS and CA-matched control groups reached significance ($p's$ > 0.05).

In sum, a similar pattern of results to that seen for the affective scenes (IAPS) was observed for the direct-gaze emotional faces, with the MA-matched controls displaying the highest SCR peak amplitudes compared to the older groups. In other words, CA most likely contributed to the significant difference seen between the MA-matched controls and the CA-matched controls, as well as the FXS participants. This interpretation is again supported by the presence of a significant spearman correlation between the overall SCR peak amplitude and CA averaged across all groups (r_{sp} = -0.673, p < 0.001)[3]. While not included as a covariate in the analyses due to the use of non-parametric tests, CA cannot explain the significant difference in SCRs observed between the FXS participants and the CA-matched controls. That is, relative to the CA-matched controls, the FXS participants displayed significantly larger SCRs to the direct-gaze faces overall, more so for disgusted facial expressions. Therefore, unlike results for the affective scenes, results for the direct-gaze faces revealed that the FXS participants displayed significant hyperarousal compared to the CA-matched controls.

Table 3

*Mean (SD) SCR amplitude and frequency for each emotional **facial expression** by group*

	FXS		MA-matched controls		CA-matched controls	
	Amplitude	Frequency	Amplitude	Frequency	Amplitude	Frequency
Happy	0.50 *(0.42)*	0.53 *(0.21)*	1.05 *(0.53)*	0.49 *(0.24)*	0.27 *(0.29)*	0.47 *(0.20)*
Sad	0.59 *(0.53)*	0.55 *(0.24)*	1.36 *(0.68)*	0.56 *(0.24)*	0.30 *(0.34)*	0.37 *(0.18)*
Angry	0.66 *(0.72)*	0.52 *(0.16)*	1.06 *(0.77)*	0.51 *(0.15)*	0.27 *(0.25)*	0.43 *(0.29)*
Fearful	0.61 *(0.55)*	0.50 *(0.18)*	1.22 *(0.67)*	0.55 *(0.17)*	0.33 *(0.30)*	0.43 *(0.20)*
Disgusted	0.73 *(0.63)*	0.56 *(0.22)*	1.13 *(0.69)*	0.55 *(0.15)*	0.31 *(0.43)*	0.39 *(0.19)*
Neutral	0.59 *(0.45)*	0.58 *(0.20)*	0.98 *(0.52)*	0.62 *(0.18)*	0.30 *(0.22)*	0.44 *(0.21)*
Overall	**0.61 *(0.50)***	**0.54 *(0.14)***	**1.13 *(0.54)***	**0.55 *(0.13)***	**0.30 *(0.26)***	**0.42 *(0.16)***

[3] No significant correlation was observed between IQ and mean SCR amplitude (Scenes: r_{sp} = 0.27, p = 0.113; Faces: r_{sp} = 0.09, p = 0.589)

Behavioural Responses

   Affective scenes. To determine whether the groups differed in their subjective ratings of the emotions evoked by the affective scenes, a mixed design, with Group (FXS, MA-matched, CA-matched) as the between-groups factor, Affective Category (happy, sad, fearful, disgusted, neutral) as the within-groups factor, and the percent of trials reported to elicit the appropriate emotion as the DV, was conducted. Greenhouse-Geisser corrected values are reported where appropriate. Results revealed significant main effects of Group [$F_{(2, 33)}$ = 4.03, p = 0.027, η^2 = 0.20] and Affective Category [$F_{(4, 75.5)}$ = 14.98, $p < 0.001$, η^2 = 0.31], as well as a significant Group by Affective Category interaction [$F_{(8, 75.5)}$ = 3.10, p = 0.016, η^2 = 0.16]. As illustrated in Figure 1, follow-up comparisons revealed that, compared to the CA-matched control group, the FXS group was significantly *less likely* to rate happy and sad images as making them feel happy (p = 0.010) and sad (p = 0.014), respectively. The FXS participants were also significantly *more likely* to rate the disgusting images as making them feel disgusted, when compared to the MA-matched controls (p = 0.001). No differences were apparent for the neutral images. The MA-matched control group was also significantly less likely than the (older) CA-matched controls to rate an image as evoking the appropriate emotion for happy (p = 0.039) and disgusting (p = 0.022) images, but more likely to report feeling fearful when viewing fearful images (p = 0.001).

   A second repeated measures ANOVA was then conducted to determine whether the groups differed in their intensity ratings of the affective scenes[4]. Results from this analysis revealed *no significant main effect* of Group [$F_{(2, 33)}$ = 1.51, p = 0.236, η^2 = 0.08] or Group by Affective Category interaction [$F_{(6, 99)}$ = 1.45, p = 0.205, η^2 = 0.08]. A significant main effect of Affective Category was observed [$F_{(3, 99)}$ = 5.56, p = 0.001, η^2 = 0.14], however, and this was explained by the fearful images being rated as significantly less intense than all the other affective images (p's $\leq$ 0.026).

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[4] Those images rated as neutral were excluded from the analysis of intensity levels.

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In sum, the behavioural results from ratings of the affective (IAPS) scenes revealed no consistent pattern of results for the FXS group compared to the two control groups. That is, the FXS group's ratings of happy images were consistent with the MA-matched control group, with both groups being significantly less likely to rate happy as making them feel happy in comparison to the CA-matched control group. In contrast, the FXS group's ratings of disgusting images were more consistent with the CA-matched control group, with both groups significantly more likely to rate disgusting images as making them feel disgusted compared to the MA-matched controls. The FXS group was also less likely to rate sad images as making them feel sad when compared to the CA-matched controls, but not the MA-matched controls. There were no group differences in the reported intensity level of the emotion experienced.
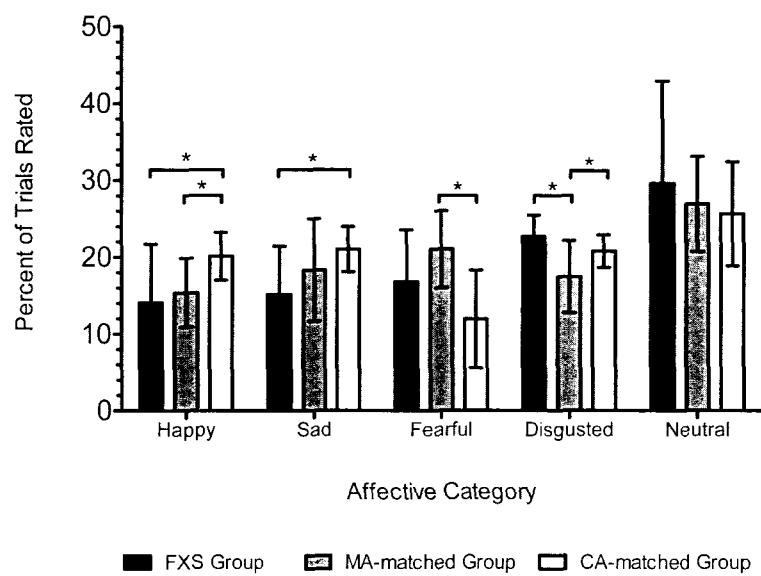

Figure 1. Group ratings of affective scenes

Direct-gaze emotional faces. Group differences in explicit emotion recognition abilities were also investigated. A mixed design, with Group (FXS, MA-matched, CA-matched) as the between-groups factor and Emotion (happy, sad, angry, fearful, disgusted, neutral) as the within-groups factor, examined the percent correct identification for each emotional expression. Greenhouse-Geisser corrected values are reported where appropriate. Results revealed a significant main effect for Group [F (2, 33) = 29.69, p < 0.001, η^2 = 0.64], such that the FXS group

performed significantly more poorly than both the MA-matched ($p < 0.001$) and CA-matched ($p <$ 0.001) control groups; and the MA-matched control group performed significantly more poorly than the (older) CA-matched control group ($p = 0.001$). A significant main effect of Emotion was also observed [F (3.06, 101.03) = 17.98, $p < 0.001$, $\eta^2 = 0.35$], with happy facial expressions being significantly easier to identify than all other emotional expressions (p's ≤ 0.005), and disgusted facial expressions being significantly harder (p's ≤ 0.020).

Results also revealed a significant Group by Emotion interaction [F (6.12, 101.03) = 7.45, $p < 0.001$, $\eta^2 = 0.31$]. As illustrated in Figure 2, this significant interaction was explained by the FXS group performing significantly more poorly than both control groups when recognising disgusted (MA-matched: $p < 0.001$; CA-matched: $p < 0.001$) and neutral (MA-matched: $p = 0.035$; CA-matched: $p = 0.015$) facial expressions. Additionally, the CA-matched control group was significantly better at recognising fearful facial expression compared to the FXS ($p = 0.001$) and (younger) MA-matched control ($p = 0.001$) groups.
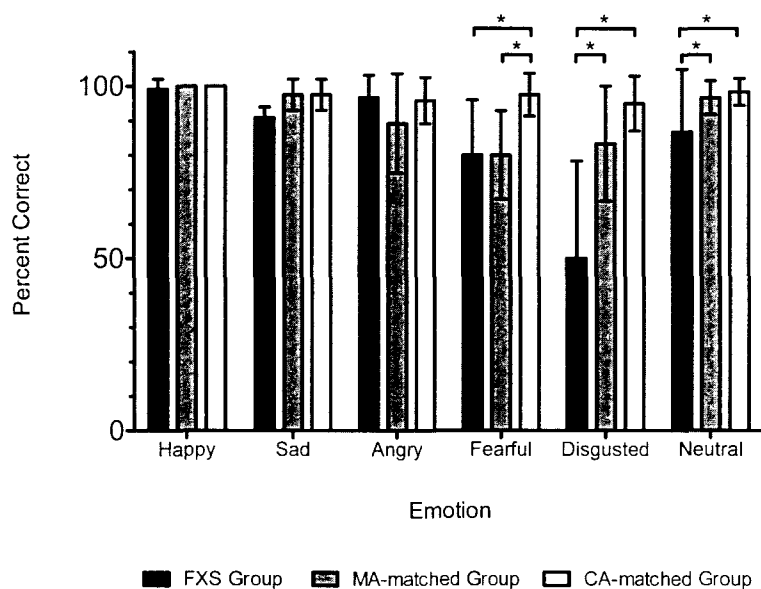

Figure 2. Emotion recognition (percent correct)

Overall, the FXS group displayed significant deficits in recognising neutral and disgusted facial expressions, but not happy, sad or angry facial expressions. The FXS group's ability to recognise fearful facial expressions was equivalent to their MA-matched peers; with the CA-

matched controls performing significantly better at recognising fearful facial expressions compared to all other groups.

<center>**Discussion**</center>

Psychophysiological Responses

Overall, the current psychophysiological findings revealed that the MA-matched control group generally had significantly higher SCR peak amplitudes for both stimulus types (affective scenes and direct-gaze emotional faces) compared to both the FXS group and their CA-matched control group. In contrast to our main prediction, no support for generalised hyperarousal in our FXS group was observed. However, the results did reveal that relative to CA-matched controls, our FXS individuals displayed significantly higher SCRs to the direct-gaze emotional faces. This finding suggests that FXS females display specific hyperarousal for socially relevant stimuli, rather than generalised hyperarousal, when compared to CA-matched peers.

Firstly, and more broadly, our overall findings suggest that sympathetic ANS responses to affective images (independent of the social relevance – that is, whether faces or evocative scenes) may attenuate with increased CA. Importantly, therefore, the developmental trajectory of the ANS may be longer than previous studies have suggested. For example, Porges and colleagues (1994) observed increased parasympathetic cardiac activity with increased age during infancy, and suggested that these parasympathetic increases represented developmental changes in the capacity of the ANS to mediate physiological and behavioural reactivity; and therefore the infants' capacity to self-regulate (Porges, Doussard-Roosevelt, Portales, & Suess, 1994). Alkon et al. (2003) later reported higher heart rates, greater sympathetic activation and increased parasympathetic withdrawal in three- to four-year-old children compared to seven- and eight-year-olds (Alkon, et al., 2003). Allen and Matthews (1997), however, reported no differences in autonomic responding between eight- to ten-year-olds and 15- to 17-year olds, suggesting that autonomic reactivity stabilises by late childhood to early adolescents (Alkon, et al., 2003; Allen & Matthews, 1997). The findings from our MA-matched control group (with a mean age of nine years) suggest that

sympathetic ANS responses, at least for affective images, may not be as stable during late childhood as previous thought.

More specifically, and with respect to FXS, the current results indicate that, in the context of normal levels of general arousal, our FXS females displayed hyperarousal specifically to more socially relevant stimuli: the direct-gaze faces. These findings are consistent with previous FXS studies, which have reported autonomic hyperarousal for social stimuli in FXS individuals compared to CA-matched controls, when using either social interactional paradigms (Belser & Sudhalter, 1995; Hall, et al., 2009) or images displaying direct-gaze faces (Farzin, et al., 2009; 2011). These results are also commensurate with behavioural studies which report social avoidance and abnormally high rates of social anxiety in the FXS population (e.g., Cohen, Sudhalter, Pfadt, Jenkins, & Brown, 1991; Hall, DeBernardis, & Reiss, 2006; Hessl, Glaser, Dyer-Friedman, & Reiss, 2006; Tsiouris & Brown, 2004). Our results provide support for the hypothesis that, within the FXS population, socially evoked hyperarousal may lead to an avoidance of, or withdrawal from, social stimuli[5].

However, our results suggest that any hyperarousal in FXS may not be as generalised as previously speculated (Cohen, 1995; Cornish, et al., 2004; Hagerman, 2002). This lack of evidence of generalised hyperarousal in our FXS group is also inconsistent with previous SCR studies which have reported hyperarousal for both non-social sensory stimuli (Hagerman, et al., 2002; Miller, et al., 1999) and when subjects perform cognitive tasks (Keysor, et al., 2002). These disparate findings may reflect differences in the experimental designs of these studies. More specifically, the studies which have reported significant hyperarousal in FXS to non-social stimuli have employed protocols involving direct physical contact with the sensory stimuli (e.g., feathers; Miller, et al., 1999), or have required the participant to actively perform a task (e.g., mental arithmetic; Keysor, et al., 2002). The current study, on the other hand, involved the passive

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[5] There were no significant correlation between either SCR amplitudes (Faces: r_{sp} = -0.16, p = 0.618; IAPS: r_{sp} = 0.06, p = 0.863) or emotion recognition (r_{sp} = 0.07, p = 0.837), with a self-report measure of social anxiety. Nevertheless, future research would benefit from using informant-report measures to investigate these relationships further.

viewing of affective images. As such, using affective *images* may not have evoked the same level of arousal as direct contact with tangible stimuli (see Hietanen, Leppanen, Peltola, Linna-aho, & Ruuhiala, 2008 for discussion). Importantly, however, the use of the passive viewing paradigm in the current study likely reduced experimenter-participant interaction during the SCR recording, therefore minimising any potential confound of increased arousal due to social interaction or performance anxiety, which may have influenced the SCRs to non-social stimuli in previous FXS studies.

An alternate explanation for the discrepancy between the current findings on general hyperarousal in FXS and those of previous studies relates to the autonomic indices used. Previous research has reported significantly higher SCLs in FXS females (Keysor, et al., 2002), particularly at baseline (Hall, et al., 2009; Keysor, et al., 2002; Roberts, et al., 2001). Consistent with Keysor and colleague's (2002) assertion, the likelihood of eliciting significant SCRs may have been reduced in the current study if the FXS group had higher tonic SCLs at baseline. As our protocol involved zeroing the skin conductance machine prior to the experimental trials in order to measure relative change in SCR, our methodology precludes us from determining whether the FXS group initially had significantly higher SCLs at baseline compared to the control groups. Having said this, however, our FXS group displayed a similar frequency of valid SCRs as the control groups, particularly the MA-matched controls, and for both stimuli set. Furthermore, we would suggest that, if the FXS group was initially hyperaroused at baseline, then the incremental increases in specific SCRs would not be as large as those seen in the controls; and more importantly, we would not have seen a significant difference when subjects viewed the direct-gaze emotional faces. As such, we think it unlikely that our methodology explains the failure to find evidence of generalised hyperarousal in the FXS subjects who took part in our study. Nevertheless, future research would benefit from including a baseline measurement of SCL in addition to specific SCRs to explicitly investigate whether higher baseline SCLs affect specific SCRs in the FXS population. Future studies also need to be conscious of potentially confounding the measurement of generalised arousal with social interaction with the experimenters.

Behavioural Responses

Affective images. Despite the MA-matched controls having larger SCRs, all three groups reported experiencing a similar degree of emotional intensity for the affective (IAPS) scenes. However, the emotion subjectively experienced by the FXS group differed depending on the valence of the image. When considering positive (happy) images, the FXS group was less likely to rate themselves as feeling happy, which was consistent with their MA-matched peers. However, when disgusting images were viewed, the FXS group's ratings were more consistent with the CA-matched control group; with both groups being significantly more likely to rate themselves as disgusted compared to the MA-matched control group. These results may be explained by the particular affective stimuli used to evoke each emotion in the affective (IAPS) stimuli. For example, happy stimuli not only included images of Mickey Mouse, puppies and ice-cream, but also images traditionally rated to evoke the "awe aspect" of happiness (e.g., landscape scene of a mountain top; see Mikels et al., 2005). As such, participants with lower MAs may have subjectively processed these images differently to those with higher MAs. For example, a person standing on top of a mountain may have evoked awe (happiness) for CA-matched controls, but fear for MA-matched controls and FXS participants.

Direct-gaze emotional facial expressions. The FXS group displayed significant emotion recognition deficits, consistent with previous research (e.g., Cornish, et al., 2005; Hagan, et al., 2008; Shaw & Porter, 2012). Specifically, while their ability to recognise happy, sad and angry facial expressions was intact, and their ability to recognise fearful faces was at their developmental level, they displayed significant difficulties recognising neutral and disgusted faces. These findings provide additional support for emerging evidence in the literature that FXS individuals display deficits in recognising neutral facial expressions, which has been reported in both the FXS full mutation (Hagan, et al., 2008; Shaw & Porter, 2012) and premutation carriers (Cornish, et al., 2005; Hessl et al., 2007). The current study is, however, the first study to report evidence of deficits in recognising disgusted facial expressions, which cannot be attributed to intellectual level, within the FXS female population. Mazzocco et al. (1994) had reported that FXS

females do not display significant deficits in recognising complex emotional facial expressions, including disgust, compared to typically developing controls once IQ is taken into account. However, the current study used a labelling paradigm rather than a picture-to-picture matching paradigm, as used by Mazzocco et al. (1994). The latter may not have been sensitive enough to pick up difficulties in emotion recognition in FXS individuals. Future research should attempt to explore the explicit emotion recognition abilities in FXS by using a range of paradigms in order to fully elucidate where the difficulty lies.

Limitations, Strengths and Future Directions

When interpreting the current findings, we need to be mindful of the limitations of the current study. Notwithstanding those mentioned above, the main limitation of this study was the small sample size and the focus on FXS females, which restricts the generalisability of the current results. The FXS literature, in general, would benefit from comparing across the FXS spectrum and taking into consideration gender, IQ, co-morbid diagnoses and genotype factors which together ultimately affect the behavioural phenotype displayed by the individual. To accomplish this, larger sample sizes are required. Particularly in a genetic disorder such as FXS, genotype factors such as Fragile X Mental Retardation Protein (FMRP) levels need to be taken into consideration when investigating the underlying causes of social impairment. Those studies which have investigated FMRP in relation to psychophysiological responding in FXS have shown mixed results. For example, Hall et al. (2009) found that higher FMRP levels in FXS females were associated with more typical heart rate variability during a social challenge protocol. Using a similar social interaction protocol, Hessl et al. (2007) reported that males with the FXS premutation, who typically produce at least some FMRP, displayed significantly reduced SCLs during the brief encounter with a stranger compared to IQ-matched controls (Hessl, et al., 2007). It is clear that this heterogeneity across the disorder needs further investigation in order to fully appreciate this genotype-phenotype relationship and associations with the processing of social and emotional information.

We also acknowledge that the stimulus choice for the affective (IAPS) scenes, which included some images depicting people, did not allow a comparison between arousal triggered by social versus non-social stimuli. Ideally, a direct comparison of SCRs to social and completely non-social stimuli may have been preferable. In fact, this had been our original intention, however, it proved pragmatically difficult to obtain affective scenes that did not depict any people, and which were appropriate for the large age range included, for certain emotional categories. Importantly, none of the affective scenes contained people with direct gaze, unlike the emotional facial expression stimuli. We would argue that direct gaze is more indicative of social engagement, whereas viewing people within a scene does not necessarily evoke the sense of social engagement within the viewer. This suggestion is supported by physiological research which has shown that direct gaze elicits stronger SCRs compared to averted gaze in typically developing individuals (Helminen, Kaasinen, & Hietanen, 2011; Hietanen, et al., 2008) as individuals with autism (Kylliainen & Hietanen, 2006). Nevertheless, it would be interesting to attempt to replicate the results reported here in relation to a dissociation between increased social arousal and normal non-social arousal in FXS. It should still be noted, however, that our results remain inconsistent with a general hyperarousal hypothesis of FXS.

Another limitation of this current study is our focus on a single measure of ANS activity. The use of a multifaceted approach may have improved the reliability of the findings, particularly if several indices measuring the pattern of both sympathetic and parasympathetic arousal simultaneously (i.e., heart rate, pupillometry, SCR) were used. While this multifaceted approach would be beneficial in future research, we note that this may be too difficult in a population, such as FXS, as this would involve attaching more equipment to already anxious individuals. Our laboratory is in the process of developing a protocol that uses remote eye-tracking and EDA to simultaneously measure eye-gaze, pupillometry and skin conductance. Hopefully, in the near future we will be able to use this protocol to further our understanding of ANS activity and eye-scan paths in FXS and other neurodevelopment disorders. Despite the potential limitations noted above, it is a strength of our study that it included both implicit and explicit measures of socio-

emotional processing, in accord with Le Doux' (2000, 1996) assertion that there are two aspects of emotion processing that always needs to be considered: the physiological process and the conscious feeling.

General Conclusion

The current findings suggest that FXS females display hyperarousal when viewing more socially salient stimuli, specifically direct-gaze emotional facial expressions, when compared to CA-matched controls, but not MA-matched controls, whose SCRs were generally larger as a consequence of their younger age. Importantly, our FXS females did not display hyperarousal to affective scenes that contain no socially salient content of this type. Together, these findings suggest that the autonomic hyperarousal observed in FXS may be social-specific rather than generalised, as previously asserted. Moreover, in addition to atypical autonomic responding to emotional faces, the FXS group displayed specific emotion recognition deficits, particularly for neutral and disgusted faces. However, atypical subjective ratings of the emotions evoked by affective scenes were also observed, despite no presence of autonomic hyperarousal in the FXS group. These results emphasize the complexity surrounding emotion processing within FXS, and highlight the need for more in-depth, multifaceted research to investigate both explicit and implicit socio-emotional processing across the FXS spectrum.

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Author Notes

Chapter 6 – Emotion Recognition and Social Approach in Fragile X Syndrome

Social Approach and Emotion Recognition in Fragile X Syndrome

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Abstract

Fragile X syndrome (FXS) is characterised by significant social impairments including: social anxiety and withdrawal, gaze aversion, and reduced interaction with peers/strangers. Moreover, there is emerging evidence that individuals with FXS display emotion recognition deficits, which may contribute to their social difficulties. The current study aimed to provide an in-depth investigation of the emotion recognition abilities of FXS individuals when processing emotional stimuli across different presentation modalities and different intensity levels. It also aimed to explore, for the first time, FXS individuals' judgements of the social approachability of other people, based on those other people's emotional cues, and after adjusting for their emotion recognition performance. Relative to chronological age- (CA-) and mental age- (MA-) matched controls, the FXS group performed significantly more poorly on the emotion recognition tasks, and displayed a bias towards detecting negative emotions, similar to that seen in individuals with social anxiety/phobia. Moreover, the FXS group displayed significantly reduced ratings of social approachability, overall, compared to both control groups; and these reduced ratings was most apparent for happy emotional expressions. These reduced social approach ratings were seen even after any emotion recognition deficits were taken into account, which suggests that social anxiety in FXS rather than poor socio-emotional processing may best explain the social avoidance and withdrawal observed in FXS.

Social Approach and Emotion Recognition in Fragile X Syndrome

The ability to accurately recognise the emotion of another person is essential for regulating our successful day-to-day social interactions, including knowing when to approach others and when it might be wise to avoid those others. For example, an inability to recognise that a stranger is angry may lead to inappropriately approaching that stranger with unfavourable consequences. Emotion recognition abilities are reportedly impaired in numerous neurodevelopmental and psychiatric disorders that are associated with disrupted social judgements and/or poor social understanding including autism, attention-deficit-hyperactivity disorder (ADHD), social anxiety, and schizophrenia, as well as in those patients with acquired brain damage (e.g., Adolphs et al., 2005; Adolphs, Sears, & Piven, 2001; Humphreys, Minshew, Leonard, & Behrmann, 2007; Mikhailova, Vladimirova, Iznak, Tsusulkovskaya, & Sushko, 1996; Pelphrey et al., 2002; Poreh, Whitman, Weber, & Ross, 1994). That emotion recognition deficits in patients with neurodevelopmental and acquired disorders might impair these individuals' abilities to make appropriate judgements regarding social interactions is supported by evidence that judgements of other people's approachability are compromised by poor emotion recognition abilities in individuals with acquired amygdala damage (e.g., Adolphs, 2003; Adolphs, Tranel, & Damasio, 1998).

Emotion recognition deficits and abnormal social approach judgements may have deleterious carry-over effects on day-to-day social functioning, such as compromised peer social interactions and relationships. One neurodevelopmental disorder that is associated with significant social impairments of this type is Fragile X syndrome (FXS), a genetically-defined neurodevelopmental disorder associated with, not only cognitive and intellectual disability, but also reduced social interaction (e.g., Cohen et al., 1988; Cohen, Vietze, Sudhalter, Jenkins, & Brown, 1991; Merenstein et al., 1996) and higher than normal rates of social anxiety (see Tsiouris & Brown, 2004). While there is emerging evidence that individuals with FXS display emotion recognition deficits (Cornish, Kogan, et al., 2005; Hagan, Hoeft, Mackey, Mobbs, & Reiss, 2008; Hessl et al., 2007; Shaw & Porter, 2012), which may contribute to their social difficulties, no

empirical research to date has investigated the social approach judgements of individuals with FXS. Specifically, no studies have investigated whether poor social approach judgements in FXS are driven by emotion recognition deficits, as appears to be the case in other neurodevelopmental disorders, such as Williams syndrome (WS), as well as in patients with amygdala damage (e.g., see Adolphs, et al., 1998; Porter, Coltheart, & Langdon, 2007).

While it seems intuitive that abnormal social approach judgements are the consequence of emotion recognition deficits, it is important to consider the co-occurrence of both in disorders that are marked by poor social relations. This is because recent evidence suggests that social approach judgements and emotion recognition abilities can dissociate. For example, Willis and colleagues (2010) recently found abnormal social judgements in conjunction with intact emotion recognition abilities in patients with orbitofrontal cortex (OFC) lesions. Such patients are characterised by a difficulty in using negative facial expressions to guide approachability ratings, in the presence of intact explicit recognition of these emotional expressions. With regard to interpreting the basis of the abnormal social approach judgements in patients with OFC lesions, it has been suggested that abnormal judgements of this type can sometimes be driven by an impairment in evaluating threat from the social environment (e.g., Willis, Palermo, Burke, McGrillen, & Miller, 2010), rather than emotion recognition deficits.

The current study aims to, firstly, provide an in-depth investigation of emotion recognition abilities in a group of FXS individuals and secondly, to investigate social approach judgements in FXS taking into consideration these individuals' emotion recognition abilities. To accomplish these aims, we explored emotion recognition abilities and social approach judgements across four different emotional expressions (happy, sad, angry and fearful) and we used five different presentation modalities (adult faces, child faces, adult voices, child voices and adult postures), as well as employing two different levels of emotional intensity (high and low), so as to increase task sensitivity.

In the following sections, we provide a general overview of FXS, before reviewing previous evidence of emotion recognition deficits and reduced social approach in FXS.

Fragile X Syndrome (FXS)

FXS is a genetic disorder that affects approximately 1 in 4,000 males and 1 in 8,000 females (e.g., Crawford, Acuna, & Sherman, 2001; Sherman, 2002; Turner, Webb, & Robinson, 1996). It results from large expansions of the cytosine-guanine-guanine (CGG) trinucleotide repeat in the promoter region of the fragile X mental retardation 1 (FMR1) gene (Frankland et al., 2004; Hatton et al., 2006; Kwon et al., 2001). In individuals with over 200 CGG repeats, the FMR1 gene is silenced and inhibits the production of the fragile X mental retardation protein (FMRP; Hagerman, 2002; Flora Tassone et al., 2000). This in turn leads to abnormal neurological and cognitive development.

Intellectual impairment is prominent in FXS. In fact, FXS is the most common hereditary cause of intellectual impairment (Feinstein & Reiss, 1998; Mazzocco, Pennington, & Hagerman, 1994). In addition to intellectual impairment, however, individuals with FXS also present with significant social impairments such as social anxiety and withdrawal, gaze aversion, and reduced interaction with peers (Cohen, et al., 1988; Cohen, Sudhalter, Pfadt, Jenkins, & Brown, 1991; Cornish, Munir, & Wilding, 2001; Hessl et al., 2001; Kaufmann et al., 2004). Similarly, the incidence of co-morbid autism, social anxiety and schizotypal personality disorder is significantly higher in FXS compared to the typically developing population (see Franke et al., 1996; Rogers, Wehner, & Hagerman, 2001; Tsiouris & Brown, 2004 for reviews). More specifically, questionnaire and interview based studies have suggested that approximately 30% of females with FXS have a social anxiety diagnosis (Franke et al., 1998) and over 20% of FXS females are reported to have a diagnosis of schizotypal and/or avoidant personality disorder (see Franke, et al., 1998; Sobesky, Hull, & Hagerman, 1994; Tsiouris & Brown, 2004). Males with FXS are also likely to display similar levels of schizoid and schizotypal features (Tsiouris & Brown, 2004). These significant psycho-social-behavioural impairments have lead FXS researchers to turn their attention to the socio-emotional processing abilities of individuals with FXS. The following section reviews evidence of emotion recognition deficits in FXS.

Emotion Recognition in FXS

Emotion recognition in FXS has been examined in relation to different presentation modalities, as discussed in the following subsections.

Facial emotion recognition in FXS. Research into the emotion recognition abilities of individuals with FXS has primarily focused on the recognition of facial emotional expressions (e.g., Mazzocco, et al., 1994; Simon & Finucane, 1996; Wishart, Cebula, Willis, & Pitcairn, 2007), with the one exception being a study by Turk and Cornish (1998), who also investigated the paralinguistic aspects of emotion recognition; that is, the recognition of emotional vocal prosody. Findings from earlier research into facial emotion recognition in FXS initially suggested no deficits amongst individuals with FXS, at least for the basic six universal emotions (anger, disgust, fear, happy, sad and surprised), with initial claims that facial emotion recognition is 'intact' in adult FXS males (Simon & Finucane, 1996), adult FXS females (Mazzocco, et al., 1994) and children with FXS (Turk & Cornish, 1998; Wishart, et al., 2007).

More recently, however, there is growing evidence that the facial emotion recognition skills of FXS individuals may not be as 'intact' as previously thought (Cornish, Kogan, et al., 2005; Hagan, et al., 2008; Shaw & Porter, 2012). These disparate findings from earlier to later studies may relate to differences in methodology. More specifically, the majority of the earlier studies employed simple picture-to-picture matching paradigms, where participants were asked to match the target emotional face to photos or schematics of emotional faces. Consequently, to successfully complete these picture-to-picture paradigms one could argue that an individual with FXS did not need to use emotion perception or knowledge of emotions, but rather could pass these tasks by solely relying on general perceptual cues. As such, these matching tasks may not be as sensitive as other emotion recognition paradigms (e.g., labelling tasks) in measuring the processes that individuals undertake when determining the facial emotional expression of fellow humans during real-world social interactions (see Hobson, 1991 for discussion).

Recent research has acknowledged these methodological issues, with interesting results. For example, Cornish and colleagues (2005) used two tests of emotion recognition with adult

male FXS carriers compared to both well-matched familial and non-familial typically developing control groups. Both tests involved labelling tasks that used a forced choice paradigm: one task used whole faces depicting the six universal emotions (happy, sad, fearful, angry, surprised, disgusted) as well as neutral expressions, while the other task depicted more complex mental states (e.g., jealous, hateful, panicked) via the eye regions of a face only (Revised Eyes Test; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Results revealed that the FXS carriers displayed poorer emotion recognition for both tasks compared to both control groups. Moreover, on the basic emotion recognition task, the deficit in the FXS carriers was most noticeable for neutral faces, which were mislabelled as one of the emotional expressions, and this deficit remained even after statistically controlling for IQ.

Consistent with Cornish et al. (2005), Hagan and colleagues (2008) also reported emotion recognition difficulties using a labelling task in conjunction with the recording of brain activity via functional imaging in a group of high-functioning females with the FXS full mutation. Specifically, the FXS group showed significantly poorer recognition of neutral facial expressions and a trend toward poorer recognition of sad facial expressions compared to typically developing females; however, there was no difference between groups for happy facial expressions. As such, Hagan and colleagues (2008) suggested that their findings of poorer emotion recognition for neutral expressions, and the trend for sad expression, in the FXS may reflect a relative difficulty recognising more ambiguous emotional facial expressions in this clinical group. Specifically, Hagan et al. (2008) argued that, as the typically developing controls took significantly longer to identify sad and neutral expressions compare to happy emotional expression, sad and neutral expressions may not be as readily identifiable as happy expression. This is consistent with previous research which has also reported happy to be the most recognisable emotional expression (e.g., Calvo & Marrero, 2009; Palermo & Coltheart, 2004).

Shaw and Porter (2012) also used a forced-choice labelling paradigm and documented specific emotion recognition difficulties in their FXS cohort compared to CA- and MA-matched controls. More specifically, the FXS participants performed significantly worse than both CA- and

MA-matched controls when recognising neutral and angry emotional facial expressions, but not happy or fearful facial expressions. Interestingly, these specific emotion recognition deficits appeared in the absence of abnormal face scanning. That is, concurrent recording of eye-movements revealed that the individuals with FXS scanned the emotional faces in a similar manner, both qualitatively and quantitatively, to the MA-matched controls but not the CA-matched controls[1].

Together, these aforementioned studies provide preliminary evidence to suggest that facial emotion recognition abilities in FXS may not be a relative strength as initially thought. Specifically, there is consistent evidence to suggest deficits in recognising neutral facial expressions, which may be more ambiguous, across the FXS spectrum (Cornish, Kogan, et al., 2005; Hagan, et al., 2008; Hessl, et al., 2007; Shaw & Porter, 2012), at least for adult faces. However, the emotion recognition ability of FXS individuals in relation to other emotional facial expressions is less clear.

Recognising emotion from vocal cues in FXS. In almost all social interactions, emotional information is communicated by multiple modalities including the face, voice and posture of the individual (Grossmann, Striano, & Friederici, 2006). It is surprising then, that only one study to date has extended the investigation of emotion recognition abilities in FXS beyond using adult facial expressions (Turk & Cornish, 1998), albeit using a matching rather than a labelling paradigm. More specifically, Turk and Cornish (1998) explored the emotion perception abilities of a group of FXS boys using two emotion cue recognition tasks, one involving recognition of emotional adult faces (happy, sad, angry, fearful) and the other involving adult vocalisations of emotion (laugh, sob, snarl, scream). Their results revealed that, compared to both a Down syndrome and a MA-matched control group, the FXS group did not display significant emotion processing deficits on

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[1] Specifically, the findings revealed aberrant scanning and reduced attention to the eyes in the FXS group, compared to a CA-matched control group. However, there were no significant differences between the FXS and MA-matched control groups in terms of the amount of time spent looking at the eye region, or the manner in which emotional faces were visually processed.

any task; however the Down syndrome group were significantly poorer at judging the likely emotions of others within different contexts compared to the MA-matched control group.

While Turk and Cornish's (1998) findings may suggest 'intact' emotion perception and attribution abilities in FXS, including when emotion is expressed via vocal cues, the tasks employed in their study may have lacked the sensitivity to identify any potential subtle emotion recognition problems due to a limited number of stimuli (that is, there was only one trial of each emotion per task). In fact, the FXS group performed lower (albeit not significantly) than MA-matched controls on the vocalisation task. Thus, the assertion that emotion perception from both faces and voices in these FXS individuals was completely intact warrants further investigation. If emotion recognition deficits are apparent in individuals with FXS, could these deficits help explain the behavioural social withdrawal characteristically observed in the disorder, as discussed below?

Reduced Social Approach in FXS

As noted earlier, heightened social anxiety, excessive shyness and social withdrawal are commonly reported anecdotally as some of the most debilitating consequences of FXS, for both the individual with FXS and their families (e.g., Kerby & Dawson, 1994; Tsiouris & Brown, 2004). Empirical research using the Developmental Behaviour Checklist (DBC; Einfeld & Tonge, 1989) has also found that young FXS individuals display significantly more shyness and avoidance of eye contact compared to intellectually-impaired controls (Einfeld, Tonge, & Florio, 1994), with these group differences remaining stable over a four year period (Einfeld, Tonge, & Turner, 1999). The findings from questionnaire-based research parallel those of these empirical studies. Both social avoidance and, specifically, eye contact avoidance have been well documented in individuals with FXS. For example in a series of studies, Cohen and colleagues (1988; 1989; 1991) revealed that gaze aversion was extreme in males with FXS, particularly when interacting with strangers. Consistent with this finding are the results of Hessl et al. (2006), who employed a social challenge protocol and found that both boys and girls with FXS displayed significant gaze aversion, overt signs of discomfort, and avoidance during social interactions with an unfamiliar adult (Hessl, Glaser, Dyer-Friedman, & Reiss, 2006). More recently, reduced eye-contact in FXS individuals,

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compared to CA-matched controls, has also been documented using eye-tracking methodology to record visual scan-paths while subjects view other people's faces (e.g., Dalton, Holsen, Abbeduto, & Davidson, 2008; Farzin, Rivera, & Hessl, 2009), although this latter pattern of data has not been replicated using MA-matched controls (see Shaw & Porter, 2012).

While avoidance during social encounters (particularly eye contact avoidance) has been well documented in individuals with FXS, studies have yet to empirically and systematically investigate whether FXS individuals are less likely to approach strangers depicting certain emotional expressions (e.g., anger), as is observed in typically developing individuals. More specifically, typically developing individuals tend to display a rank order of approachability judgements, in which they rate positive (i.e., happy) expressions as most approachable, and threatening (i.e., angry) expressions as less approachable compared to non-threatening negative expressions (e.g., sad, fearful) (see Porter, et al., 2007).

As mentioned earlier, it has been shown that social approach judgements can be influenced by emotion recognition abilities. For example, abnormal social approach judgements in patients with acquired amygdala damage appear to be a consequence of their poor emotional recognition abilities; as also appears to be the case in individuals with certain neurodevelopmental disorders such as autism and WS. In general, individuals with amygdala damage (e.g., Adolphs, et al., 1998), and those with WS (Bellugi, Adolphs, Cassady, & Chiles, 1999; Porter, et al., 2007), rate negative facial expressions as more socially approachable than do typically developing individuals. Interestingly, individuals with autism have also been reported to display this pattern of abnormally high approach ratings for negative expressions (Adolphs, et al., 2001), despite the characteristic reduced social interaction that is also observed in autism.

Of interest in the current study, therefore, was whether FXS individuals would display the normal rank order of approachability judgements, or, alternatively, whether they would display abnormal social approach judgements that were either similar to, or contrary to, the anecdotal and behavioural reports of social avoidance seen in the disorder.

Study Predictions

To reiterate, the current study had two main aims. The first was to explore, in detail, the emotion recognition abilities of a group of FXS individuals across a range of emotions, presentation modalities and levels of emotional intensity. The second aim was to empirically investigate the underpinnings of social approach judgements in individuals with FXS. Based on the literature reviewed above, it was predicted that FXS individuals would display significant emotion recognition deficits compared to both CA- and MA-matched typically developing controls. It was also predicted that the FXS group would make significantly lower social approach ratings overall and that they would not display the typical rank order of approachability. More specifically, it was predicted that FXS individuals would rate both positive and negative emotional expressions as less approachable than controls and that this group difference would not simply be due to their poor emotion recognition abilities; that is, reduced social approach would be observed even after accounting for any emotion recognition deficits. It was further predicted that the typical rank order of approachability would be attenuated in the FXS individuals.

Method

Participants

Participants were 14 FXS individuals, 14 CA- and gender-matched typically developing controls, and 14 MA- and gender-matched controls. All participants displayed normal or corrected to normal vision.

Fragile X syndrome 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 (2 male; 12 female). All FXS participants exhibited the medical and clinical phenotype associated with FXS and genetic testing confirmed the characteristic >200 CGG repeats associated with the disorder (6 Southern Blot, 8 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 FXS cohort fell in the

moderately impaired range and was consistent with the typical level of intellectual disability reported in the literature.

Typically developing control participants. CA- and MA-matched controls were recruited through the Macquarie University Kids' Science Club and via advertisements distributed across the Macquarie University campus. Exclusion criteria were a history of learning difficulties, developmental delay, intellectual impairment, as well as behavioural, psychological, sensory or cognitive deficits or a history of neurological compromise. MA and FSIQ were assessed using the WASI for control participants. Details regarding CA, MA and FSIQ for both CA- and MA-control groups are reported in Table 1. Independent-sample t-tests revealed no significant difference between the FXS and MA-matched groups on MA [t (26) = -0.50, p = 0.622] and no significant difference between the FXS and CA-matched groups on CA [t (26) = 0.10, p = 0.920].

Table 1

CA, MA and FSIQ by group

	FXS Group		CA-matched Group		MA-matched Group	
	Mean *(SD)*	Range	Mean *(SD)*	Range	Mean *(SD)*	Range
N *(% females)*	14 *(85.7%)*		14 *(85.7%)*		14 *(85.7%)*	
CA [a]	20.7 *(6.6)*	12.1–38.1	20.4 *(6.4)*	12.1–36.3	8.7 *(3.7)*	5.9–20.3
MA [a]	8.6 *(3.9)*	6.1–21.1	20.4 *(6.4)*	12.1–36.3	9.7 *(3.7)*	6.5–20.3
FSIQ [b]	64.0 *(15.1)*	51.0–96.0	107.0 *(9.0)*	91.0–121.0	107.0 *(8.2)*	97.0–126.0

[a] Mean CA and MA in years
[b] FSIQ = Standard Score (mean = 100, SD = 15)

Materials

Diagnostic analysis of nonverbal accuracy. Stimuli from the Diagnostic Analysis of Nonverbal Accuracy (DANVA; Nowicki & Duke, 1994) were used for both the emotion recognition and the social approach tasks. With regard to the former, the DANVA is a well-standardised, widely used, and psychometrically sound tool for assessing emotion recognition across different

four expressions in different modalities (faces, voices and gestures). It has good validity and reliability with data available for children from three years of age (Nowicki & Duke, 1994; psychology.emory.edu/clinical/interpersonal/DANVAmanual03.doc). The DANVA includes: 24 adult faces, 24 child faces and 40 adult postures in the form of 4" x 6" colour photographs, as well as audio tapes containing 24 adult and 24 child voices saying "I am going out of the room now, but I will be back later" in varying emotional expressions (happy, sad, angry and fearful) and varying in level of expressed intensity (high and low). Six examples of each emotion, three at each level of intensity are included. There are also 40 adult posture images, for which the entire body is shown, with the face blackened out. The posture images include eight examples of each of the four emotions listed above (four for each emotion at low and high intensity), plus an additional eight neutral gestures. The neutral gestures have not been included in the main analyses so that the same emotions could be considered across the different presentational modalities. However, the neutral gestures are analysed separately to explore whether forced biases are apparent in the groups.

Approach scale. The coloured approach scale from Bellugi, Adolphs, Cassady and Chiles (1999) was used for the current social approach task. This scale includes five alternate responses: 'yes', 'maybe', 'do not know', 'probably not', and 'no' and is reproduced in Jones et al. (2000).

Procedure

In line with Willis and colleagues (2011; 2010), the social approach task was completed prior to the emotion recognition task to ensure that there was no interference from completing the emotion recognition task on participants' social approach judgements. Participants were shown expressions in the following fixed order: adult faces, child faces, adult voices, child voices and then gestures, according to the standardised instructions in the test manual. Short breaks were provided throughout administration as required. Stimuli within a modality were presented in a fixed order, but the emotional expressions were randomized within each modality. With the stimuli on display, participants were asked to indicate how likely it was that they would go up to and ask each person for directions if they were lost in a shopping centre. Participants were given a

copy of Bellugi et al.'s (1999) colour coded approach scale (see above) to assist with their judgements. This scale was introduced and explained before use. In accord with Bellugi et al. (1999) and Jones et al. (2001), ratings were numerically coded: "yes" = 2, "maybe" = 1, "do not know" = 0, "probably not" =−1 and "no" =−2. Positive values reflected a higher likelihood of approach, while negative values indicated a lower likelihood of approach.

Following the social approach task, participants were shown each expression again in the same order as the social approach task. On this second occasion, participants were asked to say whether each expression was: "happy", "sad", "angry" or "scared" (forced choice). To reduce the load on working memory all participants were given a written list of each possible option which the investigator also read aloud on each trial. There was no time limit for a response. Error rates (mean proportion of errors) and types of error misclassifications were recorded for analysis.

Results

Greenhouse-Geisser corrections were reported where appropriate due to violations of sphericity.

Emotion Recognition

Table 2 summarises the mean proportion of errors for each group, emotion, presentational modality and level of intensity. The pattern of data suggests that the FXS group made more errors across all emotions, modalities and intensity levels compared to both MA- and CA-matched control groups. To test these effects statistically, we conducted a mixed design analysis of variance (ANOVA) with Group (FXS, MA-matched, CA-matched) as a between-groups factor, and Emotion (happy, sad, angry, fearful), Modality (adult faces, child faces, adult voices, child voices, posture) and Intensity (high, low) as within-subjects factors. Results revealed significant main effects for all variables [Group: $F (2, 39) = 20.03$, $p < 0.001$, $\eta^2 = 0.507$; Emotion: $F (3, 117) = 42.32$, $p < 0.001$, $\eta^2 = 0.52$; Modality: $F (2.83, 110.43) = 68.48$, $p < 0.001$, $\eta^2 = 0.64$; Intensity: $F (1, 39) = 322.48$, $p < 0.001$, $\eta^2 = 0.89$].

Consistent with Table 2, follow up analyses indicated that the FXS group had significantly higher mean error rates overall compared to both the MA-matched ($p < 0.001$) and CA-matched

(p < 0.001) control groups. There was also a significant difference between the control groups; MA-matched controls made significantly more errors than CA-matched controls (p = 0.019). Follow up analyses with respect to main effects of Emotion, Modality and Intensity showed that: fearful expressions were more difficult to recognise, overall, compared to all other emotions (all p's < 0.001); emotional expressions were more easily identified through facial expressions compared to voices and postures, with children's facial expression significantly better identified than adults' facial expressions (all p's < 0.001); and, not surprisingly, low intensity emotional expressions were more difficult to recognise than high intensity expressions (Intensity: p < 0.001).

Table 2

Emotion recognition: Mean proportion of errors (standard error) for each group by emotion, presentational modality and level of intensity.

	Emotion				Face		Voice		Gest.	Intensity		
Group	Happy	Sad	Angry	Fear	Adult	Child	Adult	Child	Adult	Low	High	**Overall**
FXS	0.41	0.36	0.31	0.49	0.31	0.15	0.47	0.55	0.48	0.46	0.32	**0.39**
	(0.03)	(0.03)	(0.03)	(0.04)	(0.03)	(0.02)	(0.04)	(0.04)	(0.03)	(0.02)	(0.02)	*(0.02)*
MA controls	0.20	0.19	0.23	0.52	0.21	0.07	0.39	0.37	0.38	0.36	0.21	**0.29**
	(0.03)	(0.03)	(0.03)	(0.04)	(0.03)	(0.02)	(0.04)	(0.04)	(0.03)	(0.02)	(0.02)	*(0.02)*
CA controls	0.12	0.13	0.22	0.40	0.19	0.05	0.26	0.26	0.33	0.29	0.14	**0.22**
	(0.03)	(0.03)	(0.03)	(0.04)	(0.03)	(0.02)	(0.04)	(0.04)	(0.03)	(0.02)	(0.02)	*(0.02)*
Overall	**0.25**	**0.23**	**0.25**	**0.47**	**0.24**	**0.09**	**0.37**	**0.39**	**0.39**	**0.37**	**0.22**	
	(0.02)	*(0.02)*	*(0.02)*	*(0.02)*	*(0.02)*	*(0.01)*	*(0.02)*	*(0.02)*	*(0.02)*	*(0.01)*	*(0.01)*	

The mixed ANOVA also revealed significant two-way interactions of Group x Emotion [F (6, 117) = 4.27, p = 0.001, η^2 = 0.18] and Group x Modality [F (5.66, 110.43) = 2.27, p = 0.046, η^2 = 0.10], but there was no significant Group x Intensity interaction [F (2, 39) = 0.09, p =0.915, η^2 = 0.01]. The significant two-way interactions were best explained, however, by the presence of a significant Group x Emotion x Modality interaction [F (17.03, 332.04) = 2.84, p < 0.001, η^2 = 0.13]. No other three-way interaction reached significance [Group x Modality x Intensity: F (6.46, 125.95) = 0.74, p = 0.625, η^2 = 0.04; Group x Emotion x Intensity: F (6, 117) = 0.89, p = 0.506, η^2 = 0.04]; nor did the four-way interaction when using Greenhouse Geisser correction [Group x

Emotion x Modality x Intensity: F (16.86, 328.73) = 1.55, p = 0.077, η^2 = 0.07].[2] To investigate the

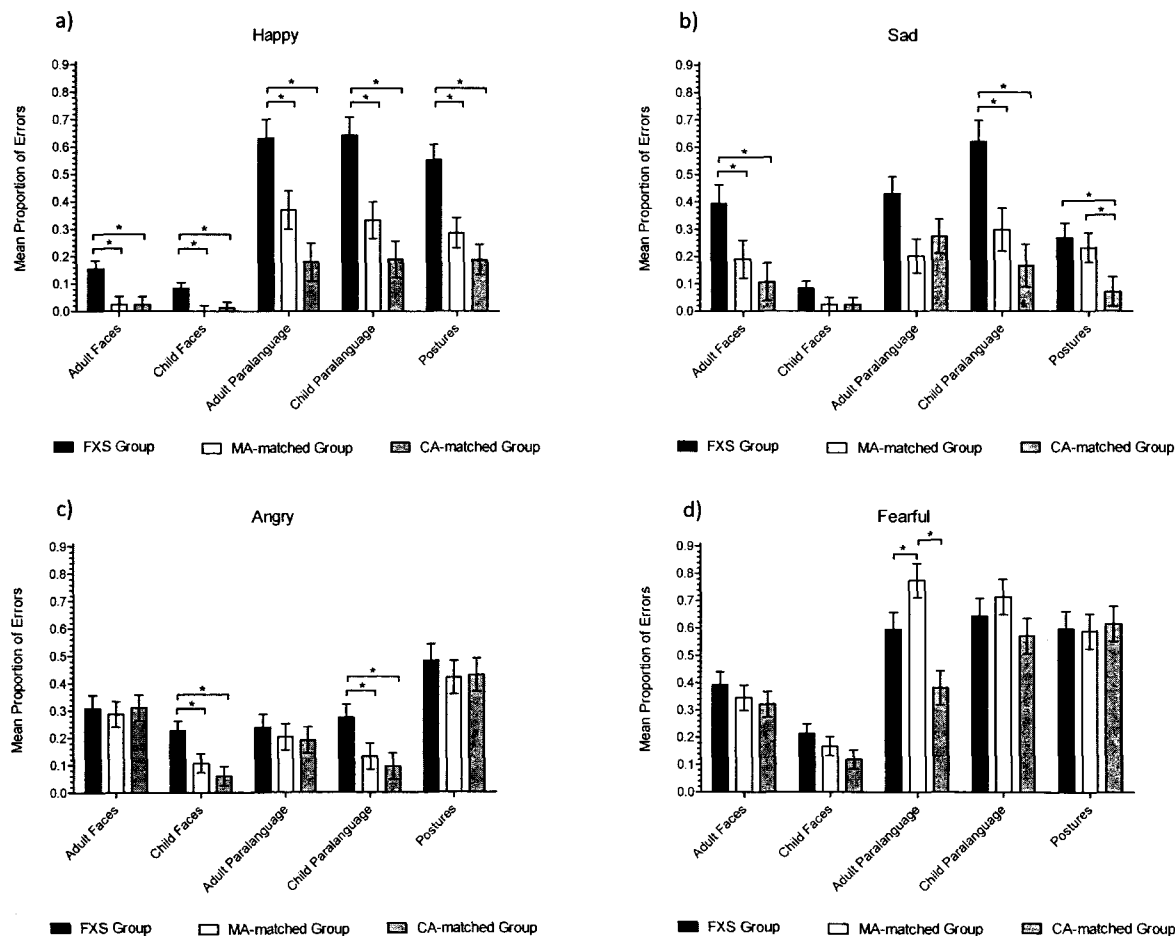three-way interaction, we broke down results by each emotion: see Figures 1a-d.

Figure 1. Mean proportion of errors for each emotion by group and modality. Error bars represent

standard error.

Figure 1a shows that, overall, the FXS group was most impaired when required to

recognise happy emotional expressions. That is, they showed a deficit relative to both control

groups and across all modalities when required to recognise happy emotions (all p's ≤ 0.019). In

contrast, The FXS group showed no impairments relative to the two control groups when required

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[2] A significant correlation was observed between IQ and overall emotion recognition (r_{sp} = -0.546, p < 0.001). As this was most likely driven by the inclusion of the two FXS males, the analyses were re-run with the two males excluded, and IQ included as a covariate. The overall pattern of results remained the same. In particular, the significant Group x Emotion x Modality interaction [F (16.52, 289.01) = 1.70, p = 0.045, η^2 = 0.08] remained, with no other significant three or four way interactions observed.

to recognise fearful emotional expressions (see Figure 1d). In fact, the FXS individuals were significantly better than the MA-matched controls at recognising the fearful expressions in adult voices (p = 0.048). Results for sad and angry emotional expressions lay somewhere in-between these two extremes. As seen in Figure 1b, the FXS group was significantly worse at recognising sad expressions in the adult faces (MA-matched: p = 0.045; CA-matched: p = 0.006) and in child voices (MA-matched: p = 0.006; CA-matched: $p < 0.001$). The FXS group was also significantly worse than the MA-matched controls (p = 0.013), but not the CA-matched controls (p = 0.084), in recognising sad adult voices. For angry emotional expressions (see Figure 1c), the FXS group was significantly worse than both control groups when presented with angry child faces (MA-matched: p = 0.020; CA-matched: p = 0.002) and angry child voices (MA-matched: p = 0.041; CA-matched: p = 0.012).

Error misclassifications. Figure 2a displays the mean percentage of all errors incorrectly labelled as happy, sad, angry or fearful respectively for each group. To further elucidate the potential presence of a response bias, a repeated-measures ANOVA with Group (FXS, MA-matched, CA-matched) as the between groups factor, Emotion (happy, sad, angry, fearful) as the within subjects factor and mean percentage of all errors misclassified as a particular expression as the dependent variable (DV) revealed a significant main effect of Emotion [F (3, 117) = 28.21, $p < 0.001$, η^2 = 0.42], a significant Group x Emotion Error interaction [F (6, 117) = 11.37, $p < 0.001$, η^2 = 0.37], but no main effect of Group [F (2, 39) = 2.98, p = 0.062, η^2 = 0.13]. Follow-up analyses revealed that the FXS group misclassified expressions as happy significantly *less* often than both control groups (p's < 0.001); and misclassified expressions as angry (p's ≤ 0.042) and fearful (p's < 0.001) significantly *more* often than both control groups. In other words, the FXS group showed evidence of a relative bias towards mislabelling expressions as angry and fearful, compared to the other groups, and away from mislabelling expressions as happy. No significant difference between the two control groups was observed with regard their profile of errors.

To further explore group differences in response biases, we also independently examined the results from the neutral gestures, which effectively served to force a bias (by having only happy, sad, angry and fearful as force-choice options). Results are displayed in Figure 2b. A mixed

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ANOVA with Group (FXS, MA-matched, CA-matched) as the between groups factor and Emotion (happy, sad, angry, fearful) as the within subjects factor and mean percentage classification for each emotion as the DV revealed a significant main effect of Emotion [F (3, 117) = 31.36, $p < 0.001$, $\eta^2 = 0.45$], a significant Group x Emotion Error interaction [F (6, 117) = 3.67, $p = 0.002$, $\eta^2 = 0.16$], but no main effect of Group [F (2, 39) = 0.50, $p = 0.610$, $\eta^2 = 0.03$]. As observed in Figure 2b, follow up analyses revealed that the FXS group was significantly *less* likely to classify a neutral gesture as happy compared to both MA-matched ($p = 0.012$) and CA- ($p = 0.002$), while being significantly *more* likely to classify a neutral gesture as angry compared to both control groups (MA-matched: $p = 0.047$; CA-matched: $p = 0.020$). They were also significantly less likely to classify neutral gestures as fearful compared to the CA-matched controls ($p = 0.016$), but not MA-matched controls ($p = 0.073$).
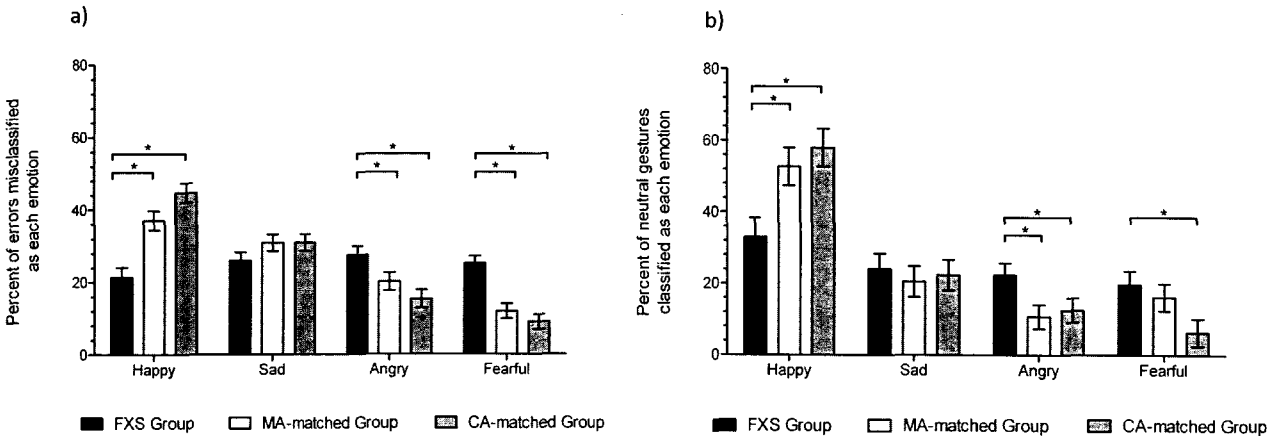

Figure 2. a) Mean percentage of errors misclassified as each emotional category. b) Mean percent neutral gestures classified as each emotional category. Error bars represent standard error.

In sum, results from the emotion recognition task revealed that compared to both CA- and MA-matched controls, the FXS participants were consistently poorer at recognising happy expressions across all modalities (they were also less likely to misclassify an emotional expression as happy). The FXS participants also displayed a significant deficit in recognising child angry expressions, as well as inconsistent difficulties in recognising sad expressions (adult sad faces and

postures, as well as child sad voices) compared to both control groups. Their relatively "intact" performance when recognising fearful emotions, and angry emotions, may have reflected their relative bias to be more likely than controls to label expressions as fearful and angry.

Social Approach

Mean ratings of approachability are displayed in Table 3. Following Porter et al. (2007) we also present the approachability ratings for only those expressions which were correctly identified on the emotion recognition task (displayed in bold). The pattern of data in Table 3 suggests that all groups were more likely to rate positive (happy) expressions as more approachable than negative (angry and fearful) expressions, whether or not we considered correct identification of the emotional expressions. As we were interested in whether the social approachability ratings differed between groups, independent of the groups' emotion recognition abilities, all subsequent analyses only considered the social approachability ratings for those expressions which were correctly identified on the emotion recognition task.

These data were analysed using a mixed design ANOVA with Group (FXS, MA-matched, CA-matched) as a between-groups factor, and Emotion (happy, sad, angry, fearful), Modality (adult faces, child faces, adult paralanguage, child paralanguage, posture) and Intensity (high, low) as the within-subjects factors. Results revealed significant main effects of Group [F (2, 39) = 19.17, $p < 0.001$, $\eta^2 = 0.50$], Emotion [F (2.42, 94.26) = 173.39, $p < 0.001$, $\eta^2 = 0.82$], Modality [F (3.51, 137.02) = 2.82, $p = 0.034$, $\eta^2 = 0.07$] and Intensity [F (1, 39) 31.89, $p < 0.001$, $\eta^2 = 0.45$]. The main effect of Group was driven by the FXS group reporting significantly lower approachability ratings overall compared to both the MA- and CA-matched control groups. The CA-matched controls also reported significantly higher approachability ratings overall compared to the MA-matched controls ($p = 0.012$). The main effect of Emotion was explained by the happy expressions being rated as significantly more approachable and the angry expressions being rated as significantly less approachable (all p's < 0.001). The significant main effect of Modality was driven by adult voices being rated as significantly less approachable compared to adult faces ($p = 0.014$), child faces ($p = 0.029$), and child voices ($p = 0.002$), but not postures ($p = 0.589$). Additionally, the

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significant main effect of Intensity revealed that, overall, high intensity emotional expressions were rated as significantly less approachable than low intensity expressions, irrespective of the emotional expression ($p < 0.001$).

Table 3

Group mean approachability ratings (standard error) for each emotion and broken down by intensity

	Happy		Sad		Angry		Fearful	
	High	Low	High	Low	High	Low	High	Low
FXS	-0.29	-0.22	-1.13	-0.94	-1.26	-1.01	-1.12	-0.72
	(0.15)	(0.16)	(0.18)	(0.20)	(0.13)	(0.17)	(0.17)	(0.16)
	0.00	**0.30**	**-1.15**	**-1.01**	**-1.38**	**-1.22**	**-1.16**	**-1.04**
	(0.17)	*(0.16)*	*(0.19)*	*(0.20)*	*(0.13)*	*(0.19)*	*(0.17)*	*(0.12)*
MA controls	0.71	0.75	-0.51	-0.22	-1.03	-0.22	-0.34	-0.37
	(0.15)	(0.16)	(0.18)	(0.20)	(0.13)	(0.17)	(0.17)	(0.16)
	0.97	**1.14**	**-0.54**	**-0.28**	**-1.05**	**-1.00**	**-0.34**	**-0.73**
	(0.17)	*(0.16)*	*(0.19)*	*(0.20)*	*(0.13)*	*(0.19)*	*(0.17)*	*(0.12)*
CA controls	1.24	1.32	-0.22	0.56	-0.87	0.32	-0.18	0.23
	(0.15)	(0.16)	(0.18)	(0.20)	(0.13)	(0.17)	(0.17)	(0.16)
	1.44	**1.68**	**-0.26**	**0.37**	**-0.97**	**-0.21**	**-0.29**	**0.00**
	(0.17)	*(0.16)*	*(0.19)*	*(0.20)*	*(0.13)*	*(0.19)*	*(0.17)*	*(0.12)*

Bolded = means *(standard errors)* when only correctly identified emotional expressions are included

Significant two-way interactions were observed between Group x Intensity [$F_{(2, 39)}$ = 10.88, $p < 0.001$, $\eta^2 = 0.36$] and Group x Modality [$F_{(7.03, 137.02)}$ = 2.13, $p = 0.044$, $\eta^2 = 0.10$]; however, the Group x Emotion interaction failed to reach significance [$F_{(4.4.84, 94.26)}$ = 2.23, $p = 0.059$, $\eta^2 = 0.10$]. Significant three-way interactions were also seen between: Group x Emotion x Intensity [$F_{(5.24, 102.24)}$ = 2.32, $p = 0.046$, $\eta^2 = 0.11$]; Group x Emotion x Modality [$F_{(18.55, 361.66)}$ = 1.82, $p = 0.020$, $\eta^2 = 0.09$]; and Group x Modality x Intensity [$F_{(7.55, 147.28)}$ = 2.10, $p = 0.042$, $\eta^2 = 0.10$]. These significant interactions were best explained by the presence of a

significant four-way interaction between Group x Emotion x Modality x Intensity [F (16.49, 321.47) = 1.85, p = 0.024, η^2 = 0.09]. As displayed in Figure 3, we separated the data by emotion to aid with interpretation.

Happy. As illustrated in Figure 3a, compared to both MA- and CA-matched controls groups, the FXS group was significantly less likely to approach happy expressions across all face and voices at all intensity levels (p's ≤ 0.027). For happy postures, a significant difference was only observed between the FXS and CA-matched control groups and then only for low intensity happy postures (p < 0.001). No significant group differences were observed for high intensity happy postures (p's ≥ 0.161).

Sad. The FXS group's ratings of approachability for sad expression was variable compared to the other groups (Figure 3b). Compared to both MA- and CA-matched control groups, the FXS group were significantly less likely to approach sad adult faces and sad adult voices at *low* intensity (p's ≤ 0.002), with all groups finding high intensity sad adult faces and voices equally unapproachable. In contrast, it was only the high intensity sad child faces and sad child voices that the FXS group was significantly less likely to approach (p's ≤ 0.043). For postures, the FXS group only differed from the CA-matched controls.

Angry. There were no differences between the FXS group and the MA-matched controls for angry emotions (see Figure 3c). The FXS group only reported significantly lower approach ratings compared to the CA-matched control group for angry adult faces at both intensity levels (p's < 0.006), low intensity child faces (p = 0.003) and low intensity adult postures (p = 0.028).

Fear. As shown in Figure 3d, the FXS group rated children's high and low intensity fearful faces as significantly less approachable compared to both MA- and CA-matched control groups (p's < 0.039). This difference was also seen for children's fearful voices, but only at the high intensity (p's < 0.004). The FXS group's approachability ratings were equivalent to those of the MA-matched controls, but significantly less than the CA-matched controls for fearful: adult faces at all intensity levels (p's < 0.019), low intensity child voices (p = 0.005) and low intensity adult postures (p = 0.020).
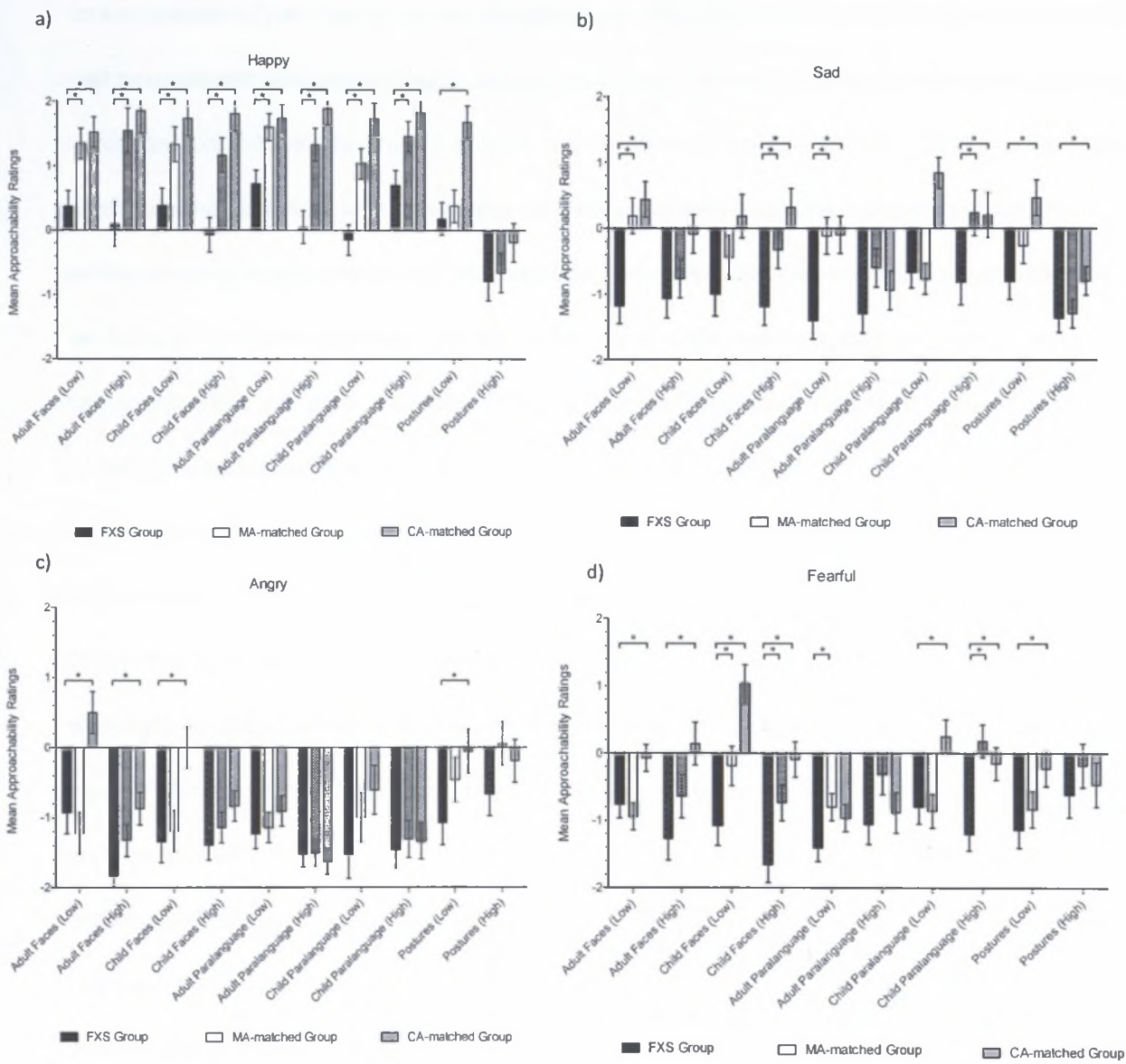
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Figure 3. Group mean approachability ratings by intensity and emotion. Positive values (above the x-axis) represent approachable, negative values (below the x-axis) represent unapproachable

In sum, even after emotion recognition deficits were taken into consideration, the data from the social approach judgements revealed that the FXS group displayed significantly reduced approach ratings, overall, compared to both MA- and CA-matched controls. This was most apparent for happy expressions across all modalities of presentation, although it was also observed to a lesser extent for sad and fearful expressions. There were also some variable effects on the FXS group's approachability ratings of intensity levels across the different modalities of

presentation. For example, the FXS group found the high intensity sad and fearful expressions of children, whether conveyed via face or voice, as less socially approachable than the MA- and CA-matched controls.

In order to investigate the effect of gender bias and IQ on social approach behaviour, we re-ran the analysis with the FXS males excluded, and IQ included as a covariate. In contrast to the emotion recognition analysis, once IQ was controlled for, the significant four-way interaction between Group x Emotion x Modality x Intensity [F (15.85, 277.32) = 1.02, p = 0.440, η^2 = 0.05] became non-significant. This suggested that the abnormal social approach behaviour observed in FXS individuals may result from their level of intellectual impairment.

Discussion

The current study aimed to investigate the emotion recognition abilities of individuals with FXS using expressions conveyed via different modalities of presentation and at varying levels of intensity, and then to explore social approach judgements of those same stimuli in FXS when emotion recognition difficulties were taken into consideration.

In line with our first prediction, the FXS individuals in the current study displayed significant emotion recognition deficits when compared to both MA- and CA-matched controls. Specifically, our FXS participants displayed a consistent deficit in recognising happy expressions across all modalities, along with a specific deficit for recognising expressions of anger portrayed by children. There was also some evidence of a deficit in recognising sad emotional expressions; although no obvious pattern across the different modalities was apparent. In contrast, there was no evidence of a deficit in recognising fearful facial expressions. At the same time, however, there was also evidence for different biases across groups when misclassifying emotions. That is, relative to both control groups, the FXS group displayed a significant bias towards labelling emotional expressions as fearful, whilst displaying a bias away from labelling emotional expressions as happy. This response bias may indeed explain the pattern of emotion recognition results observed. Importantly, these specific emotion recognition deficits remained even after controlling for IQ (and gender biases).

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In terms of their social approach judgements, the FXS group displayed the typical rank order of approachability (i.e., rating happy expressions as more approachable relative to negative expressions) after having taken into account any emotion recognition deficits. Once modality of presentation and intensity levels were also taken into account, however, some differences across the emotions did become apparent when the FXS group was compared to the two control groups. The FXS individuals' approachability ratings for happy expressions were significantly reduced compared to both MA- and CA-matched controls, irrespective of presentation modality. Similarly, the FXS group rated high intensity sad and fearful expressions of children's faces and voices as less socially approachable than both control groups. In contrast, the FXS group varied little from the two control groups when rating the approachability of angry facial expressions; that is, all groups gave low approachability ratings for such expressions. Interestingly, unlike the emotion recognition deficits, these group differences in social approach ratings could be explained by IQ.

The implications of our findings in relation to previous research are discussed in the following subsections.

Emotion Recognition

As our study was the first, to date, to investigate emotion recognition abilities in FXS using different presentation modalities and varying levels of emotional intensity (high versus low), comparisons can only be made between our results and those from previous studies for the adult facial expressions; and to an extent, adult voices.

Happy expressions. The current study is the first to report a deficit in recognising happy expressions in FXS; and this deficit was, in fact, striking. Our result here appears inconsistent with previous FXS research reporting evidence of intact recognition of happy emotional voices (Turk & Cornish, 1998) and faces (e.g., Wishart, et al., 2007), even when including those studies which have reported some deficits in facial emotion recognition (Cornish, Kogan, et al., 2005; Hagan, et al., 2008; Shaw & Porter, 2012). These inconsistencies may result from differences in the FXS populations and the experimental tasks used in each study. For example, Cornish et al. (2005) investigated emotion recognition abilities in FXS premutation carriers, who typically display

relatively intact general intelligence and a more subtle FXS clinical phenotype (for example see Franke, et al., 1998; 1999). The premutation carrier's milder FXS phenotype may, therefore, include less profound emotion recognition difficulties which resulted in findings of an intact ability to recognising happy facial expressions in that study.

However, both Hagan et al. (2008) and Shaw and Porter (2012) also reported no deficit in recognising happy facial expressions in individuals with the FXS full mutation, although deficits in recognising neutral facial expressions were present in these studies. As the FXS cohorts of Hagan et al. (2008) and Shaw and Porter (2012) are similar to those used in this current study, the implication is that the discrepant findings are more likely to reflect the different stimuli used across these studies. One possibility in this regard is that the use of emotional expressions of both low and high intensity in the current study made for a more difficult task compared to previous studies (e.g., Cornish, Kogan, et al., 2005; Hagan, et al., 2008; Shaw & Porter, 2012). Therefore our study may have been more sensitive in picking up any potential emotion recognition deficit in the FXS group. We do not, however, believe differences between our current results and those of previous studies simply reflect greater general task difficulty in our own study. This is particularly so because our participants had an unlimited time to respond, and both our control groups (and most importantly the MA-matched controls) displayed similar, if not lower, error rates compared to Hagan et al., (2008) and Shaw and Porter (2012).

We do acknowledge, however, that the absence of neutral expressions in the current study (with the exception of the neutral gestures) may have impacted on the results reported here. In more detail, the bias towards labelling emotional expressions as negative may have had more of an impact on the recognition of happy expressions in the current study due to the lack of any neutral facial and vocal expressions being presented. Indeed, in previous FXS emotion recognition studies, there have been apparent deficits in recognising neutral facial expressions (e.g., Cornish, Kogan, et al., 2005; Hagan, et al., 2008; Shaw & Porter, 2012), which may reflect a negative response bias similar to that observed in the current study. This assertion is supported by the presence of a significant bias towards perceiving negative emotions for the neutral

gestures included in the current study. As such, by not including neutral faces or voices in the current study, any potential negative bias may have indeed been picked up more by the happy expressions, resulting in the FXS group showing relatively poorer performance of these expressions, compared to the control groups.

Fearful expressions. The finding that the current cohort of FXS individuals did not display a deficit in recognising fearful expressions most likely reflects the significant response bias towards labelling expressions as fearful seen in the group relative to both the CA- and MA-matched control groups. This negative response bias is commensurate with findings from the social anxiety literature.

Several studies have found that individuals with clinical and sub-clinical levels of social anxiety/phobia are more likely to display a bias towards identifying others' emotional expression as negative (e.g., Bell et al., 2011; Winton, Clark, & Edelmann, 1995). Moreover, socially anxious individuals are also reported to selectively attend to threat relevant stimuli more quickly than non-threatening stimuli (e.g., Gilboa-Schechtman, Foa, & Amir, 1999; Purcell, Stewart, & Skov, 1996). As individuals with FXS characteristically display heightened levels of social anxiety (Tsiouris & Brown, 2004), the presence of a negative bias of the type found in the current study is not surprising. Only one previous study of emotion recognition in FXS has investigated misclassifications, with no evidence of a negative bias observed in that case (Shaw & Porter, 2012). The disparate findings between the current study and that of Shaw and Porter may reflect differences in task sensitivity; with the current study including more presentation modalities and intensities of expression, and also varying age of the actor displaying emotions. The presence of negative biases within the FXS population, and the association between these potential biases and levels of social anxiety warrant further investigation, particularly if treatment for social anxiety can remediate the emotion recognition deficits observed in the FXS population.

Angry and sad expressions. The indication of some deficits in recognising angry and sad emotional expressions is somewhat consistent with previous behavioural studies (Hagan et al., 2008; Shaw & Porter, 2012). Shaw and Porter (2012), for example, found a specific deficit in

recognising high intensity adult angry facial expressions in their FXS cohort compared to MA- and CA-matched controls, but unlike the current study, no deficit for high intensity sad facial expressions was found in that study. Hagan and colleagues (2008), on the other hand, observed a trend for poorer recognition of sad facial expressions in their FXS cohort. Again, we suggest that the sensitivity in using both high and low intensity examples of emotional expressions in the current study may have allowed for subtle problems in recognising sad and angry emotional expressions (across different presentation modalities) to be detected. This possibility is commensurate with Hagan et al. (2008), who suggested that individuals with FXS may have difficulty with more ambiguous emotional expressions. To clarify, the inclusion of low intensity emotional expressions in our study most likely heightened the ambiguity of emotions expressed.

Difficulties with recognising angry (e.g., Calder et al., 1996) and sad (e.g., Blair, Morris, Frith, Perrett, & Dolan, 1999) emotions have been associated with amygdala dysfunction. The angry and sad recognition deficits observed in the current FXS cohort therefore appear to be commensurate with recent imaging studies that have reported amygdala dysfunction in individuals with the FXS pre-mutation (Hessl, et al., 2007) and full mutation (Gothelf et al., 2008; Hazlett et al., 2009; Watson, Hoeft, Garrett, Hall, & Reiss, 2008). Importantly, however, our FXS group did not display a significant deficit for fearful expressions, which is characteristic of amygdala patients (e.g., Adolphs, 1999; Adolphs, et al., 2005), although as mentioned above, a relative bias in the FXS group may have mitigated against our finding evidence of a deficit in recognising fearful expressions. Shaw and Porter (2012) also reported no deficit in recognising fearful expressions. Additionally, our FXS group's deficits in recognising sad and angry expressions were not consistent across presentation modalities or intensity levels, which makes us hesitant to suggest that the pattern of performance on our behavioural task is consistent with that seen in patients with amygdala dysfunction.

The amygdala, however, is highly interconnected with other brain regions which also play a role in emotion processing including the frontal lobes (Damasio, Anderson, & Tranel, 2011). As such, it is possible that the emotion recognition difficulties apparent in our FXS group may have

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resulted from a disruption between the neural pathways which connect the limbic and frontal regions. Frontal lobe functional abnormalities have been noted in individuals with FXS (see Lightbody & Reiss, 2009 for a review); including, but not limited to, reduced activation of the OFC (Tamm, Menon, Johnston, Hessl, & Reiss, 2002) and ACC (Hoeft et al., 2007) during tasks that tap inhibitory control (e.g., Stroop and Go/No-Go tasks). With regard to the current study findings, the patterns of both the emotion recognition deficits and the misclassification of errors (which differed from controls who displayed a happy bias) observed in our FXS group may provide some support for this suggestion of a contribution to emotional recognition deficits in FXS from frontal dysfunction. In other words, it is possible that the current results reflect generalised frontal-related emotion recognition problem in FXS rather than discrete deficits or biases for specific emotions. To clarify, generalised emotion recognition deficits have been reported in patients with the frontal variant of fronto-temporal dementia (fvFTD; Keane, Calder, Hodges, & Young, 2002; Rosen et al., 2004). For example, Rosen and colleagues (2004) reported that, while both patients with fvFTD and the temporal variant (tvFTD) displayed significant deficits in recognising negative emotions, the fvFTD group also displayed a deficit in recognising happy expressions. These authors speculated that this behavioural pattern may have been due to the more pervasive damage to the frontal lobes, and in particular the OFC and/or anterior cingulate cortex (ACC) in the fvFTD group. Both the OFC and ACC have been implicated in the poor recognition of emotions by other patient studies (Heberlein, Padon, Gillihan, Farah, & Fellows, 2008; Willis, et al., 2010) and those using typically developing individuals (e.g., Blair, et al., 1999). Indeed, Blair and colleagues (1999) specifically reported that viewing angry facial expressions was associated with enhanced activity in the OFC, whereas increasing intensity of both angry and sad facial expressions was associated with increased ACC activation in the fvFTD group.

Although our findings need to be interpreted with caution due to the small sample sizes, and any suggestions made can only be speculative due to the lack of supportive neuroimaging and (neuro)psychological data, we raise the possibility that the pattern of emotion recognition deficits seen in the FXS participants may reflect frontal lobe dysfunction and/or heightened levels of

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social anxiety. Future research is required to further investigate the role that the frontal lobes may play, as well as to elucidate the influence of social anxiety, on the emotion recognition abilities of FXS individuals. However, this suggestion, that frontal lobe dysfunction may explain the emotion recognition problems seen in FXS, is generally commensurate with the view of Cornish and colleagues (2004), who have suggested that the cognitive, behavioural and social phenotypes seen in FXS may all be explained by core impairments in executive inhibitory control with subsequent inability to effectively regulate arousal (Cornish, Sudhalter, & Turk, 2004).

Social Approach Behaviour

The findings from the data for social approachability judgements revealed that the FXS group, on a whole, judged strangers as less approachable, and that this heightened avoidance was apparent across all emotional expressions. Specifically, even after taking into consideration the FXS group's apparent difficulty with recognising happy emotional expressions, the FXS group still rated approaching individuals portraying happiness as less likely, independent of the presentation modality (face or voice), age of the other person expressing emotion (adult or child) and level of intensity of emotion. This pattern of approachability judgements is in stark contrast to the task performances and behaviour of 'hyper-social' individuals with WS, who also display intellectual impairment (e.g., Bellugi, et al., 1999; Porter, et al., 2007), as well as patients with amygdala (e.g., Adolphs, et al., 1998) or OFC (Willis, et al., 2010) damage. These latter groups have all been reported to rate strangers displaying negative emotions as more approachable than controls. As such, the pattern of social approach ratings in FXS individuals, discussed above, appears inconsistent with the putative effects of OFC or amygdala dysfunction (e.g., see Blair, et al., 1999), and may relate, in part, to their level of intellectual impairment.

Interestingly, individuals with high functioning autism have also been reported to rate negative facial expressions as more approachable than controls, consistent with the ratings of individuals with amygdala damage (Adolphs, et al., 2001). These "hyper" approach ratings are seen despite the well-known behavioural phenotype of autism, which is characterised by reduced interactions with other people (American Psychiatric Association, 2000). So, while in day-to-day

life, both FXS individuals and those with autism display similar levels of social withdrawal (particularly with respect to strangers), their empirical judgements of social approach appear to differ dramatically. It is unclear why individuals with autism display such a disparity between their social approach ratings and their actual social behaviour; however, the latter may relate more to their noted significant difficulty with higher-level social cognition (Adolphs, et al., 2001), which would result in a lack of understanding of the mental lives of others in autism, and hence an autistic wariness of others as "un-understandable". On the other hand, while FXS individuals have also been reported to display some higher-level social cognition deficits, such as difficulties attributing false beliefs (Cornish, Burack, et al., 2005; Garner, Callias, & Turk, 1999), these deficits are much less severe than those seen in autism (see Cornish, Burack, et al., 2005). Therefore, FXS individuals may make social approach judgements that are more commensurate with their actual behaviour in social interactions because of their relatively better social cognition abilities to understand what is going on inside other people's minds. We suggest that the current findings provide empirical support for a general avoidance of strangers in FXS, and indirect support for the suggestion that this social withdrawal is independent of any impairment in socio-emotional processing, and might be explained, in part, by this population's heightened social anxiety (Tsiouris & Brown, 2004). This suggestion is consistent with the FXS group's performance on the emotion recognition task; that is, their increased bias towards mislabelling emotional expressions as fearful or angry.

Limitations and Future Directions

The findings reported here need to be interpreted cautiously and with limitations of the study in mind. Firstly, the sample size included in the current study was relatively small with respect to other FXS research. This small sample size was primarily due to difficulties recruiting FXS participants. Focusing on increasing the sample size in future studies will provide the avenue to investigate emotion recognition abilities and social approach judgements in more detail. Specifically, it is important to take into account the heterogeneity within the FXS population and to investigate how socio-emotional processes are influenced by factors such as gender, CGG

repeats, FMRP levels and activation ratios, all of which are known to influence FXS individuals' cognitive and behavioural functioning (see Hagerman, 2002 for a review). For example, FMRP expression is prognostically important (Tassone et al., 1999) and is associated with the degree of amygdala dysfunction in FXS (Hessl et al., 2011). Thus, focusing on FMRP levels may provide further insight into the molecular markers associated with socio-emotional abilities.

Another limitation of the current study was the lack of converging neuropsychological and neuroimaging data. Future research would benefit from including standardised neuropsychological measures, particularly those that tap specific executive functions such as inhibitory control and mental flexibility (e.g., Stroop, Haylings, Trails B). This approach would allow researchers to directly investigate Cornish et al.'s (2004) suggestion that a deficit in inhibitory control, in addition to arousal dysregulation, can explain the socio-emotional responding of FXS individuals. The inclusion of a measure of social anxiety would also be informative and may potentially reveal a relationship between social anxiety levels, biases in emotion recognition, and the degree to which FXS individuals fail to approach others. In a similar vein, concurrent measures of neural activation and/or autonomic arousal during emotion recognition and social approach tasks would also allow researchers to investigate the relationships between performance on explicit tests of emotion recognition and social approach and the functioning of specific brain regions, as well as levels of autonomic arousal, all of which underpin socio-emotional decision making processes. This line of future research may ultimately elucidate whether or not the amygdala and/or specific frontal regions, or even other brain regions, are important for successful emotion recognition and judicious social approach behaviours and how disruptions to these mechanisms might explain the abnormal social behaviours seen in FXS.

General Conclusion

To date, this current study is the only one to empirically investigate emotion recognition abilities in FXS individuals across different presentation modalities and intensity levels. It is also the first to explore the social approach judgements of FXS individuals after adjusting for their

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emotion recognition performance. The current findings provide general support for recent research, which has noted emotion recognition deficits across the FXS spectrum (Cornish, Kogan, et al., 2005; Hagan, et al., 2008; Shaw & Porter, 2012). Emotion recognition problems were observed in the FXS group, predominately for happy emotional expressions, and, to a lesser extent, sad and angry expressions. It was suggested that this pattern of recognition deficits may be best explained by frontal dysfunction and/or social anxiety.

The social approach judgements made by the FXS individuals in this study were generally consistent with anecdotal and behavioural reports of social withdrawal in this disorder (e.g., Cohen, et al., 1988; Hessl, et al., 2006); that is, when compared to the two control groups, the FXS group rated strangers as less approachable, overall, and this was particularly so for happy strangers. These reduced social approach ratings were seen even after taking into account any emotion recognition deficits in the FXS group, which suggests that social anxiety, or level of intellect, rather than socio-emotional processing difficulties may best explain social withdrawal in FXS. Such a proposal is also consistent with the suggestion of a bias towards recognising fear and away from recognising happy when in doubt about another person's expression, a pattern also seen in individuals with social anxiety.

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Chapter 7 – General Discussion

General Discussion

Overall, this thesis aimed to provide an in-depth investigation of socio-emotional processing in FXS. More specifically, the four empirical papers comprising this thesis explored explicit and implicit aspects of emotional processing within a group of FXS individuals, as well as the more general social processing abilities of FXS, initially in contrast to WS individuals. Paper One adopted a broad cross-syndrome approach by investigating social attention in FXS and WS. Specifically, the attentional mechanisms underlying the visual processing of naturalistic social scenes were compared in these two disorders and the findings highlighted some interesting differences. The remainder of the thesis then moved on to focus exclusively on FXS in order to better specify the nature of socio-emotional processing in this population. Papers Two and Three each explored explicit facial expression recognition within this disorder, whilst also investigating different components of implicit emotional processing – visual attention (visual scan-paths) and autonomic arousal (skin conductance responses; SCRs), respectively. These two papers reported some of the first studies to empirically investigate both explicit and implicit emotional processing simultaneously in the FXS population. Paper Four then provided insight into the social approachability judgements made by FXS individuals, after taking into account any emotion recognition deficits. The findings provided empirical evidence consistent with the characteristic social aversion seen behaviourally in FXS individuals.

The purpose of this general discussion is to summarise the main findings from each paper, and address the implications of these findings as a whole. Limitations of the current research are also considered, and avenues of future research are discussed.

Overview of Findings

Paper One: Viewing Social Scenes: Comparing FXS and WS

Paper One employed eye-tracking methodologies to investigate the attentional processes that underpin social processing within FXS and WS. It is the first study, to date, to manipulate the location of social information within naturalistic scenes to directly compare the competing

hypotheses of attentional capture and attentional disengagement, as well as considering general attentional engagement, in either the WS or FXS populations.

Social Attention in WS. The findings from Paper One were in partial support of the growing body of evidence that suggests individuals with WS display difficulties in disengaging attention away from socially salient information (e.g., Porter, Shaw, & Marsh, 2010; Riby, Doherty-Sneddon, & Bruce, 2009; Riby & Hancock, 2008); rather than having their attention more captured by social information (Tager-Flusberg, Plesa-Skwerer, Schofield, Verbalis, & Simons, 2007). The WS group spent significantly *more* time attending to social information when presented immediately at fixation compared to all other groups, but spent *less* time attending to social information which was not immediately available. Moreover, the WS group also took longer, albeit not significantly, to disengage attention away from directly presented social information, compared to all other groups. Together, these findings suggest that the WS individuals displayed increased attention to directly presented social information, consistent with the argument that attentional disengagement difficulties may play a role in the WS social phenotype (e.g., Mervis, 2003; Porter, et al., 2010; Riby, et al., 2009; Riby & Hancock, 2008, 2009). Moreover, the reduced overall attention given to social information presented in the periphery in the WS group also provides indirect evidence against the attentional capture hypothesis of WS, as suggested by Tager-Flusberg and colleagues (2007).

Social Attention in FXS. With respect to FXS, the main focus of this thesis, the findings suggest that FXS individuals actively avoid social information, at least initially. In more detail, the FXS group were observed to disengage their attention away from directly presented social information significantly more quickly than all other groups. These results are consistent with anecdotal and observational reports of social avoidance/anxiety within the FXS population, as well as behavioural and eye-tracking studies which have focused specifically on eye contact aversion in FXS (Dalton, Holsen, Abbeduto, & Davidson, 2008; Farzin, Rivera, & Hessl, 2009; Holsen, Dalton, Johnstone, & Davidson, 2008; Tsiouris & Brown, 2004). Importantly, however, the FXS group did attend to social information over time, unlike the pattern seen in socially anxious

individuals (see Mogg, Bradley, de Bono, & Painter, 1997). That is, the FXS group attended to social information overall to a similar degree as the MA- and CA-matched controls, suggesting some habituation to the social information over time within the FXS group.

Overall, the findings from Paper One suggest that diverging social attentional processes in FXS and WS may underlie the distinct social phenotypes that characterise these two neurodevelopmental disorders.

Paper Two: Emotional Face Scanning in FXS

As noted above, the results of Paper One suggested that FXS individuals actively avoid social information, at least initially. Moreover, previous FXS eye-tracking studies have suggested that FXS individuals avoid the eye regions of emotional faces; however, none of these previous studies have included either a MA-matched control group, or measures of explicit emotion recognition (Dalton, et al., 2008; Farzin, et al., 2009; Farzin, Scaggs, Hervey, Berry-Kravis, & Hessl, 2011; Holsen, et al., 2008). Based on these methodological limitations of previous studies, and the findings of Paper One, Paper Two employed eye-tracking methodology to specifically investigate automatic visual scanning of emotional facial expressions (neutral, happy, angry and fearful), in addition to explicit emotion recognition abilities, in FXS individuals compared to typically developing CA- and MA-matched controls. This paper aimed to concurrently document the explicit emotion recognition abilities of FXS individuals, while exploring how FXS individuals visually process emotional facial expressions. It also investigated the relationships between these variables and measures of social anxiety, schizotypy and autism features in FXS.

Findings from Paper Two revealed that the FXS group displayed specific emotion recognition deficits for angry and neutral facial expressions, compared to both CA-matched, and more importantly, MA-matched controls. No negative bias, however, was observed in the FXS group in this instance. Despite the presence of these specific emotion recognition deficits, the eye-tracking findings revealed that, while the FXS group scanned emotional faces both quantitatively and qualitatively in ways that differed to the CA-matched controls, their visual scan-paths were similar to those of the MA-matched controls. Specifically, the FXS group spent

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the same amount of time attending to the eye regions of emotional faces, and visually scanned the emotional faces in the same manner as the MA-matched controls. While these findings are consistent with those from previous eye-tracking studies of FXS which have included CA-matched controls (Dalton, et al., 2008; Farzin, et al., 2009; 2011), the inclusion of the MA-matched controls in Paper Two provided evidence of a general developmental delay, rather than a specific deficit in scanning emotional facial expressions in the FXS individuals. Paper Two also revealed that earlier initial fixation on, and longer viewing of, the eye regions were associated with overall explicit emotion recognition in the FXS group; as was our index of holistic processing in this study (i.e., mean run count, in which a 'run' refers to attention to and then away from an area of interest, such as the eyes). In addition, autistic features in FXS were *negatively* correlated with recognition of happy expressions and, interestingly, social anxiety symptoms were *positively* associated with time spent attending to the eye region.

Paper Three: Hyperarousal in FXS Females

To recap, findings from Paper Two revealed that our FXS individuals displayed difficulties in explicit facial emotion recognition above and beyond their developmental level, in the presence of developmentally appropriate visual scanning of these same emotional faces. These findings suggest that aberrations in other implicit processes in FXS may better explain the socio-emotional difficulties observed within the disorder. Previous FXS research has asserted that autonomic hyperarousal may be one such implicit process which is aberrant in FXS, and which may, in turn, explain the FXS socio-behavioural phenotype (Cohen, 1995; Cornish, Sudhalter, & Turk, 2004; Hagerman, 2002). It has been suggested that the social impairments, including the autistic tendencies and social anxiety, seen in FXS are secondary to generalized hyperarousal that leads to an avoidance of, or withdrawal from, socially salient stimuli (see Cornish, et al., 2004). Paper Three sought to explore the presence of generalised and/or more social-specific hyperarousal in a group of FXS females. More specifically, SCRs were recorded while FXS females, as well as both CA- and MA-matched controls, were presented with two sets of visual images of arousing stimuli: direct-gaze faces and affectively arousing scenes. While the affective scenes occasionally depicted

people's bodies, none depicted direct faces; and as such, it was expected that the direct-gaze

faces would be more socially salient than the affective scenes.

In Paper Three it was hypothesised that the FXS group would display generalised

hyperarousal (i.e., that this group would display significantly larger SCRs than both control groups

irrespective of stimulus set), but that this hyperarousal would be particularly heightened for the

more socially salient information (i.e., the direct-gaze faces). The effect of the different emotions,

expressed in the faces and evoked by the affective scenes, on SCRs was also investigated by

manipulating the emotional categories used within each stimulus set. Overall, the

psychophysiological findings provided no support for generalised hyperarousal in our group of FXS

females. Rather, the MA-matched control group generally displayed significantly larger SCRs for

both stimulus types (affective scenes and direct-gaze emotional faces) compared to both the FXS

and CA-matched control groups; suggesting that SCRs habituate with age. However, our FXS

females did display significantly larger SCRs to the direct-gaze emotional faces, relative to the CA-

matched controls. These results suggested that, when compared to CA-matched peers, FXS

females display specific hyperarousal for more socially relevant stimuli, rather than any

generalised hyperarousal as previously reported (e.g., Cornish, et al., 2004). In addition to the

observed hyperarousal to direct-gaze emotional faces, the FXS group also displayed specific

deficits in explicit emotion recognition, particularly for disgusted and neutral faces; partially

consistent with Paper Two. Moreover, despite the absence of generalised autonomic

hyperarousal in the FXS females, atypical subjective ratings of the emotions evoked by the

affective scenes were observed.

Paper Four: Socio-emotional Processing in FXS

Thus far, both Papers Two and Three of the current thesis reported explicit emotion

recognition difficulties within FXS. While deficits in recognising neutral facial expressions were

present across the two studies, the remaining emotion-specific difficulties were more

inconsistent. That is, Paper Two reported difficulties in recognising angry facial expression,

whereas Paper Three reported intact recognition of angry faces, but difficulties in recognising

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disgusted faces in FXS females. These results suggested that explicit emotion recognition in FXS requires further investigation. Moreover, previous studies of emotion recognition in FXS, including those discussed thus far in the current thesis, have focused primarily on facial emotion recognition (e.g., Mazzocco, Pennington, & Hagerman, 1994; Simon & Finucane, 1996; Wishart, Cebula, Willis, & Pitcairn, 2007; although see Turk & Cornish, 1998). As such, Paper Four aimed to investigate the emotion recognition abilities of individuals with FXS using expressions conveyed via different modalities of presentation (face, body, voice), different ages of the other person (adult, child) and at varying levels of intensity (high and low). It also aimed to explore social approach judgements of those same stimuli in the FXS individuals, when their emotion recognition difficulties were taken into consideration.

Results from Paper Four again revealed significant emotion recognition deficits in FXS individuals when compared to both MA- and CA-matched controls. Specifically, in contrast to Papers Two and Three, the FXS group included in Paper Four displayed a consistent deficit in recognising happy expressions across all modalities. Interestingly, they were also less likely to misclassify an emotional expression as happy. Partially consistent with the results of Paper Two, the FXS group also displayed a specific deficit for recognising expressions of anger, but only when portrayed by children. There was also some evidence of a deficit in recognising sad emotional expressions; although no obvious pattern across the different modalities was apparent. In contrast, there was no evidence of a deficit in recognising fearful facial expressions. This relatively "intact" performance when recognising fearful and angry emotional expressions, most likely reflected the FXS group's relative bias to be more likely than both control groups to label expressions as fearful and angry.

Moreover, after taking into account the aforementioned emotion recognition difficulties in the FXS group, these individuals were observed to display a typical rank order of social approachability ratings, similar to that seen in controls. That is, they rated happy expressions as more approachable relative to negative expressions. Overall, however, the FXS individuals judged the various stimuli of strangers as less approachable than both CA- and MA-matched controls, and

this heightened avoidance was apparent across all emotional expressions. Even after taking into consideration the FXS group's difficulty with recognising happy emotional expressions, the FXS group were still less likely to rate people displaying happy expressions as approachable, independent of the presentation modality, age of the stranger, and level of intensity. As such, Paper Four was one of the first studies to empirically document this heightened avoidance, commensurate with the observational and behavioural reports of the social avoidance that is considered characteristic of FXS individuals (e.g., Cohen et al., 1988; Hessl, Glaser, Dyer-Friedman, & Reiss, 2006). Moreover, the FXS group's performances on not only the emotion recognition task, but also on the social approach task, are consistent with the performances of individuals with social anxiety.

The following section discusses the implication of these findings as a whole.

Implications of Findings

Explicit Emotional Processing

Overall, the FXS individuals who took part in this thesis research consistently displayed deficits in explicit emotion recognition compared to both CA- and MA-matched controls (see Papers Two, Three and Four). Whilst inconsistent with early reports of intact emotion recognition in FXS (Mazzocco, et al., 1994; Simon & Finucane, 1996; Turk & Cornish, 1998; Wishart, et al., 2007), these results are consistent with those emerging more recently in the FXS literature, specifically, those studies which have more recently reported facial emotion recognition difficulties in individuals with the FXS full mutation (Hagan, Hoeft, Mackey, Mobbs, & Reiss, 2008), as well as in those with the FXS premutation (Cornish, Kogan, et al., 2005). The current findings also provide a novel contribution to the literature by revealing that these emotion recognition difficulties extend beyond faces. That is, deficits in explicit emotion recognition were also noted for emotional voices and bodies (Paper Four); a finding which is in contrast to previous reports, for voices at least (see Turk & Cornish, 1998). More importantly, perhaps, is that the inclusion of a gender- and MA-matched control comparison group (in addition to a gender- and CA-matched control group) also allowed the current studies to elucidate that these emotion recognition

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deficits cannot be fully explained by a general level of reduced intellect in FXS. Findings pertaining to specific emotional expressions are reported below.

Positive expressions. With the exception of Paper Four, the general pattern of results from the current thesis suggests that the ability to recognise happy expressions remains intact within the FXS population. This pattern is consistent with both previous FXS research (Mazzocco, et al., 1994; Turk & Cornish, 1998; Wishart, et al., 2007), as well as the general emotion recognition literature, which reports that, for typically developing individuals, happiness is the easiest and quickest emotion to recognise (e.g., see Palermo & Coltheart, 2004). It is somewhat unclear, however, why the results from Paper Four are so disparate from these previous findings, with a stark deficit in recognising happy expressions across all modalities (face, body, voice) observed in FXS individuals in this case. This paper was also the first to detect a bias away from labelling expressions as happy in FXS. These novel findings, while somewhat inconsistent with previous results, may reflect the increased sensitivity of the tasks used in the study reported in Paper Four, and, in particular, the inclusion of low intensity representations of emotional expressions, as well as multiple modalities, which have not been well researched before in the FXS literature. Moreover, it is possible that the FXS individuals' responses on the emotion recognition task in Paper Four may have been influenced by their responses on the social approach task. That is, FXS individuals may understand that happy expressions can be approached, but as, they reported heightened avoidance irrespective of the emotional expression portrayed, this may have influenced their later recognition of these same emotions. Future research would benefit from manipulating the task order of emotion recognition and higher-order social judgement tasks to investigate their respective influence on FXS individuals' performances on each other task.

Neutral expressions. The findings from this thesis revealed that FXS individuals display a consistent deficit in recognising neutral expressions (Papers Two and Three), compared to both CA- and MA-matched controls, and a potentially related deficit in recognising the only non-negative expression in Paper Four (i.e., happy expressions). This finding related to neutral expressions is consistent with the emerging FXS literature, which has reported deficits in

recognising neutral expressions across the FXS spectrum (Cornish, Kogan, et al., 2005; Hagan, et al., 2008; Hessl et al., 2007). This deficit could be explained, as suggested by Hagan and colleagues (2008), by difficulties in recognising emotional expressions that are more ambiguous in nature. That is, FXS individuals may in fact have difficulties in interpreting ambiguous social information, similar to that seen in individuals with social anxiety, who are reported to interpret ambiguous social information as threatening (Bell et al., 2011; Mogg, et al., 1997). This suggestion is interesting in light of the heightened levels of social anxiety observed in the FXS population (Tsiouris & Brown, 2004). In particular, whilst Paper Two reported generalised misclassification of errors across emotions, rather than a negative bias for ambiguous expressions, the results from Paper Four provided indirect support for such a bias, by revealing that FXS individuals were more likely to misclassify an *emotional* expression as fearful relative to both control groups. Moreover, when forced to classify *neutral* gestures as either: happy, sad, angry or fearful, the FXS individuals displayed a bias towards labelling gestures as angry. Whilst it is unclear why a negative bias was observed in Paper Four but not in Paper Two, this difference may relate to the differential sensitivity of the stimuli used in the two studies and power issues. That is, Paper Two only included six high intensity examples of each of the four emotions, in comparison to the ten of each high and low intensity exemplars across three different modalities used in Paper Four. Thus, Paper Two may not have been sensitive enough to pick up biases in responding given the relatively limited stimulus set.

Nevertheless, the current findings provide additional empirical evidence consistent with the emerging literature that suggests individuals across the FXS spectrum have difficulty in recognising neutral facial expression, potentially due to their inherent ambiguity. This pattern of results suggests that the heightened levels of social anxiety seen in this disorder may explain this group's difficulty in recognising neutral expressions. Future research is required to replicate the presence of a negative bias in FXS, and to extend the investigation of ambiguous emotional expressions presented via different modalities, such as bodies and voices.

Negative expressions. Results pertaining to the explicit recognition of negative emotional expressions were variable. Overall, the FXS group's ability to recognise sad expressions remained relatively intact, although some fluctuation in performance was observed. Similarly, recognition of fearful expressions was found to be intact across all studies; however, the presence of a bias toward labelling emotions as fearful (Paper Four) suggests that these intact performances need to be interpreted with some caution. Disgusted expressions were only investigated in one study (Paper Three), and only for facial expressions. However, the findings from this study indicated that, at a minimum, FXS females have difficulties in recognising faces portraying disgust. As disgust can be considered to be a complex emotion, which is easily confused with other emotions, the innate ambiguity surrounding disgusted expressions may have hindered the FXS individuals' explicit recognition of this emotion (see Palermo & Coltheart, 2004 for further discussion on the confusability of emotions). This suggestion is in line with the FXS group's reported difficulties in recognising neutral expressions. Finally, with respect to angry expressions, while there was some suggestion that the recognition of angry expressions was impaired in the FXS group (see Papers Two and Four), this result again was not consistently seen across studies (e.g., Paper Three) or across presentation modalities (e.g., Paper Four).

Taken together, the findings from this thesis suggest that individuals with FXS display variable deficits in recognising negative emotional expressions; with deficits being more apparent for angry and disgusted expressions compared to sad and fearful ones. The inconsistency seen across the tasks employed in this thesis and the emotions used makes it difficult to definitively interpret the findings with respect to theories of neural dysfunction in FXS. Patients with amygdala damage are reported to display a selective deficit in recognising negative emotional expressions, particularly fear (e.g., Adolphs, Tranel, & Damasio, 1998; Adolphs, Tranel, Damasio, & Damasio, 1994; Back, Ropar, & Mitchell, 2007). While, this deficit in FXS is not always the case (see Hamann et al., 1996), I would be hesitant to suggest that the current pattern of deficits seen in this FXS cohort is specifically consistent with the pattern observed in patients with amygdala damage. Based on the current results, it is possible that dysfunction in frontal-limbic and/or

frontal-striatal pathways, more generally, may explain the emotion recognition difficulties observed in the FXS groups studied in this thesis. Moreover, the suggestion of generalised frontal-related and inconsistent recognition abilities in FXS is putatively consistent with the hypothesis of general disinhibition in responding in FXS, as supported by reports of inhibitory control difficulties within the disorder (e.g., Cornish, et al., 2004).

In sum, the current thesis provides empirical evidence of emotion recognition deficits in FXS compared to both CA- and MA-matched controls, and across multiple modalities of expression. These deficits appear particularly apparent for ambiguous emotional expressions, and, in some cases, negative expressions. Future research should aim to elucidate whether these deficits are best explained by heightened levels of social anxiety and/or frontal dysfunction, in order to inform the development of specific remediation programs with a view to improving social functioning in FXS in daily life.

The following section turns to discussing the implications of the implicit emotional processing findings from this thesis.

Implicit Emotional Processing

In contrast to the aforementioned findings regarding explicit emotion recognition in FXS, the FXS individuals studied in this thesis did not display significant deficits in implicit emotional processing. More specifically, while the current findings revealed that FXS individuals display aberrant visual scan-paths and autonomic hyperarousal compared to CA-matched controls, importantly, these differences were not seen when the FXS individuals were compared to MA-matched controls. These results suggest, therefore, that at least these aspects of implicit emotion processing are at developmentally appropriate levels in FXS.

To my knowledge, Paper Two is the first study to include MA-matched controls when investigating visual scan-paths of emotional facial expressions in FXS. As such, while the finding that FXS individuals spent less time attending to the eye regions of emotional faces relative to CA-matched controls is consistent with the literature (Dalton, et al., 2008; Farzin, et al., 2009; 2011; Holsen, et al., 2008), the amount of time they spent attending to the eyes did not differ

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significantly from their MA-matched peers. Interestingly though, while visual scanning of emotional faces in isolation was found to be equivalent to MA-matched peers, FXS individuals were noted to display more avoidance of social information in scenes, when compared to these MA-matched controls, at least initially (Paper One). The discrepancy between these sets of findings is of interest, particularly as one might predict that, the more socially salient the stimuli (i.e., the direct-gaze emotional faces), the more the FXS individuals would actively avoid, due to the more aversive nature of the stimuli. Indeed, this premise is supported by the findings of Paper Three, in which FXS females displayed significantly higher autonomic arousal for direct-gaze emotional faces compared to the more generally arousing affective scenes. Overall, the FXS group visually attended to social information within social scenes across time to a similar degree as both control groups; suggesting habituation to the social information over time. Thus, compared to more general social information, it may be that viewing direct-gaze emotional faces in isolation leads to an initial increase in autonomic arousal (Paper Three), but as it is harder to avoid the direct social stimuli, this may lead to quicker habituation to such stimuli over time (suggested in Paper Two). This potential for habituation over time is also of interest, as this is a pattern not typically seen in individuals with social anxiety (e.g., Mogg, et al., 1997). These findings, suggestive of habituation to social stimuli over time, may simply reflect lower levels of social anxiety in FXS compared to individuals with a formal diagnosis of social anxiety/phobia; or alternatively, these findings may suggest that the mechanisms underlying avoidance in FXS versus social anxiety may in fact be dissociable. This possibility warrants further investigation, particularly in light of the significant social anxiety reported in FXS (Tsiouris & Brown, 2004).

As mentioned above, the current cohort of FXS females displayed significant autonomic hyperarousal (as indexed by SCRs) compared to CA-matched, but not MA-matched peers, and only for the more socially salient stimuli (i.e., the direct-gaze emotional faces). This finding is contrary to reports that FXS individuals display generalised hyperarousal, which in turn, leads to social avoidance (e.g., Cohen, 1995; Cornish, et al., 2004; Hagerman, 2002). Moreover, whilst previous FXS research has reported that FXS individuals display significant hyperarousal for non-

social stimuli (e.g., Hagerman et al., 2002; Keysor, Mazzocco, McLeod, & Hoehn-Saric, 2002; Miller et al., 1999) in addition to social interactions (Hall, Lightbody, Huffman, Lazzeroni, & Reiss, 2009; Hessl, et al., 2006), the non-social tasks used in these previous studies need to be considered more closely. None of these non-social paradigms controlled for experimenter-participant interaction, thus making it difficult to definitively determine if autonomic arousal was generalised, or due to the task context and the inherent social experimenter-participant interaction and/or performance anxiety, which is characteristic of social anxiety disorders. Future research would therefore benefit from directly comparing autonomic arousal for social and non-social stimuli, with this methodological issue in mind, to further elucidate whether hyperarousal in FXS in generalised, or related to more socially salient information, as suggested by the current results. Moreover, including multiple indices in future research to measure both sympathetic and parasympathetic arousal would be beneficial. For example, combining eye-tracking with skin conductance methodologies to measure autonomic arousal (via pupillometry and SCRs, for example) simultaneously with visual scan-paths would provide a detailed analysis of arousal levels at the exact point of time when specific stimuli are attended to. Ultimately, including concurrent neuroimaging alongside eye-tracking and autonomic recordings would also provide real-time neuropsychophysiological responses; however, I acknowledge that this approach would be difficult with the FXS population.

Overall, these implicit emotional processing findings suggest that visual scanning of, and autonomic arousal in response to, emotional faces is aberrant in FXS when compared to CA-matched peers, but is equivalent to that of MA-matched peers. These findings are, interestingly, in contrast to the performances of FXS individuals when making socio-emotional judgements, as discussed below.

Socio-emotional Evaluative Judgements

Findings from the current thesis revealed that the socio-emotional judgements made by FXS individuals are aberrant, relative to both CA- and MA-matched controls. Importantly, these abnormal social judgements were seen, even when emotion recognition deficits in FXS were

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taken into consideration, and even in the absence of significant implicit emotional processing difficulties. Overall, these findings experimentally index the striking social avoidance which has been reported anecdotally and observed behaviourally in FXS individuals (Cohen, et al., 1988; Hessl, et al., 2006). These findings concerning socio-evaluative judgements also suggest that social anxiety levels may explain the social avoidance observed in FXS over and above their observed socio-emotional processing deficits. This is not to say that higher-order socio-emotional deficits are not present within the disorder. Rather, based on the FXS individuals' approachability ratings (Paper Four), as well as their aberrant subjective ratings of emotions evoked by affective scenes (Paper Three), it is quite clear that FXS individuals have difficulties in making higher-order social judgements. That is, they appear to have difficulties in using implicit emotional information, which has been shown to be at developmentally equivalent levels in FXS, in order to inform their judgements about their own subjective feelings (subjective ratings; Paper Three) and about the social approachability of other people (social approach ratings; Paper Four).

These results also fit with findings from earlier studies using perceptual matching tasks, which showed intact emotion perception in FXS (e.g., Mazzocco, et al., 1994; Simon & Finucane, 1996; Turk & Cornish, 1998; Wishart, et al., 2007). Taken together, the results from this thesis, and those of previous studies, suggest that lower-level perceptual and implicit processing of emotional expressions is generally intact in FXS. However, when required to explicitly recognise (label) an emotional expression, or interpret emotional expressions to inform social behaviour, individuals with FXS display significant difficulties that cannot be explained away by their lower level of general intellect. While one could assert that difficulties in recognising/labelling emotions could result from simple language deficits, language abilities have been reported to be relatively intact in the FXS population (e.g., Freund & Reiss, 1991). Thus, I suggest that individuals with FXS may have difficulties at the level of interpreting the emotional perceptual information and integrating that information with one's own motivations and desires to ultimately act in socially appropriate ways, which aligns with Adolphs' (2001) concept of normal *social cognition*. This suggestion is consistent with previous research which has reported theory of mind deficits in FXS

that are comparable to those seen in Down syndrome (Cornish, Burack, et al., 2005); although it has been suggested that these theory of mind deficits may be explained by generalised executive dysfunction in FXS, including disinhibition (Grant, Apperly, & Oliver, 2006).

Future research should employ a cognitive neuropsychological approach to investigate each level and aspect of emotional processing to better identify and localise where the difficulties specifically lie for the FXS population, or, are more likely for the FXS individual.

Strengths, Limitations and Future Directions

Strengths

Overall, this thesis revealed that FXS individuals display aberrant social attention (Paper One) compared to both CA- and MA-matched controls, as well as individuals with WS. Additionally, this thesis provided empirical evidence of emotion recognition deficits within the FXS full mutation population, which has been refuted in the past (e.g.,Turk & Cornish, 1998; Wishart, et al., 2007). Emotion recognition deficits were observed across Papers Two through Four; all of which used different standardised stimulus sets. Importantly, the FXS group's emotion recognition deficits were apparent when compared to both CA- and MA-matched controls. In contrast, abnormal visual scanning of emotional facial expressions (Paper Two) and significant autonomic hyperarousal for social-specific stimuli (Paper Three) were observed only relative to CA-matched controls. Moreover, even when the observed emotion recognition deficits in FXS were taken into consideration, the FXS individuals continued to display abnormal social judgements of emotional expressions relative to both control groups (Paper Four), consistent with the behavioural social aversion that is characteristic of FXS; and seen in social anxiety more generally.

The studies in this thesis are some of the first to investigate socio-emotional processing in FXS by including both a CA- and a MA-matched control group. This approach allowed, for the first time, consideration of whether the FXS group's performances across tasks could be explained by a general developmental delay or a specific deficit. In addition to the advantage of including both a CA- and a MA-matched control group, the current studies also benefited from investigating both explicit and implicit emotional processes simultaneously in FXS. Whilst these are considerable

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strengths of the current research I also acknowledge that there are several limitations of this research that need also to be considered.

Limitations

One major limitation of the current thesis relates to the sample sizes used across the four studies. I acknowledge that these sample sizes are relatively small, and therefore, limit the generalisability of the reported findings. However, the use of small sample sizes is a common limitation when studying most clinical samples; and, even more so in FXS studies, given the social difficulties that FXS individuals face. Because of the latter, this group can lack a willingness to participate in research. Having said this, the current sample sizes are reasonably comparable to other neuropsychophysiological studies reported in the FXS literature (e.g., Farzin, et al., 2009; Farzin, et al., 2011; Hagan, et al., 2008; Holsen, et al., 2008). Nevertheless, the issue surrounding difficulties with recruitment of FXS individuals for research purposes is one that FXS researchers as a whole, particularly in Australia, need to begin to address; as discussed at the recent Fragile X Association of Australia Research Symposium, Brisbane, October 2011.

Related to this difficulty in recruiting FXS participants, another limitation of the current thesis is the heterogeneity of the FXS cohort. Originally, this thesis aimed to focus on investigating socio-emotional processing in females with the full mutation, but in order to increase power, FXS males were also included in some of the studies. There are inherent problems with including both FXS females and males within the same studies, particularly with respect to the relative severity of intellectual impairment across genders in FXS and appropriate control matching. Future research would benefit from increasing the sample sizes in order to better compare FXS males and females. Moreover, by increasing the sample size, future research could also investigate other important factors in addition to gender, such as chronological age, genotype, and level of cognitive ability, all of which may affect socio-emotional processing. In particular, there is emerging evidence that suggests FXS premutation carriers, like individuals with FXS, also display relative socio-emotional processing difficulties (e.g., Cornish, Kogan, et al., 2005; Hessl, et al., 2007). Thus, it would be of interest to investigate further the effect of genotypic diversity, for example, by exploring the

associations between cytosine-guanine-guanine (CGG) repeat sizes and/or Fragile X Mental Retardation Protein (FMRP) levels and socio-emotional functioning. As no genetic information was included in the current thesis these relationships could not be investigated.

Future Directions

Several future directions have already been highlighted throughout this general discussion. Here, I focus on four areas of future research, which I believe have the potential to further the literature on socio-emotional processing in FXS, and in turn, ultimately inform treatment programs.

Firstly, the results from the current thesis leave many questions unanswered, particularly pertaining to implicit emotional processing in FXS. Future research should begin to employ a multifaceted approach to investigate the psychophysiology underpinning implicit socio-emotional processing across the FXS spectrum. As mentioned above, the concurrent recording of eye-tracking and indices of both sympathetic and parasympathetic autonomic activity may further elucidate whether implicit emotional processing is, as suggested from the current results, relatively spared; or is, in fact, impaired to some degree. Moreover, if it is determined that there are impairments in implicit emotional processing in FXS, the next step is to include concurrent neuroimaging alongside the psychophysiological measures to explore whether specific neural regions (e.g., amygdala, OFC) or pathways (e.g., fronto-limbic, fronto-striatal) are implicated in aberrant socio-emotional processing in FXS.

The second, related area of future research concerns hyperarousal in FXS. The findings from this thesis suggest, contrary to previous reports, that autonomic hyperarousal in FXS females is only observed for more socially salient stimuli, and only relative to CA-matched peers and not MA-matched peers. The FXS community would benefit from researchers exploring this finding further to better elucidate the nature of hyperarousal in FXS, keeping in mind the aforementioned methodological issues related to this type of research. Once the nature of autonomic hyperarousal is well-defined in FXS, targeted treatment programs can begin to be developed. However, treatment programs may differ depending on the nature of the hyperarousal in

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different FXS individuals; for example, generalised hyperarousal may benefit from pharmaceutical treatments (e.g., see Hagerman, et al., 2002), whereas, if hyperarousal is found to be related to more socially salient stimuli, then systematic desensitization therapy may be more appropriate.

The third line of future research which would be interesting to pursue relates to clarifying the influence that social anxiety has on socio-emotional processing in FXS. The findings from this thesis suggest that heightened levels of social anxiety may explain, at least to some degree, the socio-emotional processing deficits observed in FXS individuals. However, it is noted that some aspects of the FXS groups' performances were disparate to the performances that are typically seen in individuals with social anxiety. Including a social anxiety comparison group in future FXS research may therefore help to tease apart the specific similarities and differences seen in these two disorders.

Finally, as mentioned above, I believe we need to consider cognitive neuropsychological approaches for the next phase of research into socio-emotional processing in FXS. That is, in order to better elucidate the nature and extent of socio-emotional processing difficulties across the FXS spectrum, researchers need to systematically investigate each specific aspect of emotional processing, from lower-level face and other sensory perception through to emotion expression identification, and finally higher-order social judgements and decision-making following such identification. This sort of comprehensive investigation will allow for the better identification of specific deficits, which, due to the phenotypic diversity seen within the disorder, may differ between FXS subgroups and individuals. Again, using this sort of cognitive neuropsychological approach to localise the specific deficit or deficits in FXS individuals will, in turn, inform treatments to target the specific aspects of socio-emotional processing that require remediation. A long-term goal could ultimately be to develop individualised treatment programs to remedy the social difficulties that different FXS individuals face in their daily life.

Concluding Remarks

In sum, the findings reported in this thesis suggest that a comprehensive understanding of socio-emotional processing in FXS may be more complex than initially thought. Overall, the

findings of this thesis suggest that, in the presence of relatively intact implicit emotional processing, FXS individuals display deficits in explicit emotional cue processing, in conjunction with abnormal higher-order social judgements. These findings lead the way for further research into the mechanisms that underpin socio-emotional processing within the disorder. In particular, a worthwhile goal may be to turn our focus towards multi-dimensional and holistic approaches to investigate these socio-emotional processes, while also considering the influence of social psychological factors such as social anxiety. As our understanding of these socio-emotional deficits increases, we can ultimately turn our attention to individualised intervention and treatment programs to either remediate or compensate for the social difficulties faced by FXS individuals in their daily lives.

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