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Prefrontal social cognition network dysfunction underlying face encoding and social anxiety in fragile X syndrome

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Abstract

Individuals with fragile X syndrome (FXS) commonly display characteristics of social anxiety, including gaze aversion, increased time to initiate social interaction, and difficulty forming meaningful peer relationships. While neural correlates of face processing, an important component of social interaction, are altered in FXS, studies have not examined whether social anxiety in this population is related to higher cognitive processes, such as memory. This study aimed to determine whether the neural circuitry involved in face encoding was disrupted in individuals with FXS, and whether brain activity during face encoding was related to levels of social anxiety. A group of 11 individuals with FXS (5 M) and 11 age- and gender-matched control participants underwent fMRI scanning while performing a face encoding task with online eye-tracking. Results indicate that compared to the control group, individuals with FXS exhibited decreased activation of prefrontal regions associated with complex social cognition, including the medial and superior frontal cortex, during successful face encoding. Further, the FXS and control groups showed significantly different relationships between measures of social anxiety (including gaze-fixation) and brain activity during face encoding. These data indicate that social anxiety in FXS may be related to the inability to successfully recruit higher level social cognition regions during the initial phases of memory formation.

Keywords

fragile X syndrome; social anxiety; face encoding; subsequent memory; brain function

Introduction

Fragile X syndrome (FXS) is the most common known cause of inherited intellectual disability, affecting 1 in 4,000 males and 1 in 6,000 to 8,000 females. FXS results from disruption of the FMR1 gene and reduced Fragile X Mental Retardation Protein (FMRP) expression, leading to

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a phenotype encompassing cognitive, behavioral, and emotional functioning. Individuals with FXS have intellectual disability, hyperactivity, attention deficits, autistic behaviors, and social anxiety (Hagerman and Sobesky, 1989; Lesniak-Karpiak et al., 2003; Reiss and Dant, 2003). Level of FMRP expression in FXS has been suggested to indicate underlying pathogenesis of the disorder. Although FXS is caused by disruption of a single gene, recent findings support the idea that FXS is a spectrum disorder, given the varying effects of FMRP expression patterns which lead to a continuum of behavioral symptoms (Belmonte and Bourgeron, 2006).

Social anxiety is commonly cited as one of the core characteristics of fragile X syndrome. Individuals with FXS display several behaviors indicative of social anxiety, including increased time to initiate social interactions, poor eye contact, shyness, aberrant social greeting behavior, and decreased accuracy in judging direction of gaze (Garrett et al., 2004; Hagerman and Sobesky, 1989; Lesniak-Karpiak et al., 2003; Turk, 1992; Wolff et al., 1989). In addition, hyperarousal and difficulty modulating arousal level may be related to anxiety in social situations in FXS (Belser and Sudhalter, 1995; Cohen, 1995; Hall et al., 2006; Hessl et al., 2006). Although individuals with FXS appear to be interested in social interaction, both failure to maintain eye contact and awkward social behaviors often prevent the formation of meaningful relationships outside of the family (Kau et al., 2004).

Extant literature on fragile X syndrome indicates a marked association with autism. Approximately 15-25% of individuals with FXS are also diagnosed with autism (Bailey et al., 1998; Rogers et al., 2001), and a greater percentage display characteristics of autism, including repetitive behavior, deficits in interpersonal socialization skills and non-verbal communication, and dysfunction in social play with peers (Freund et al., 1993; Hagerman et al., 1986; Reiss and Freund, 1992). Several theories have been proposed to account for this association, with some suggesting that the individuals with FXS who also have a diagnosis of autism (FXS+ASD) and those without autism (FXS-only) are different on the basis of cognitive and social profiles. Others propose that autistic behavior and FXS co-occur in most individuals with FXS, but on a continuum of mild to severe, such that those with FXS+ASD are not qualitatively different from those with FXS-only (Bailey et al., 2004; Lewis et al., 2006).

Several issues contribute to this debate. First, demographic variables, especially gender, have not been examined thoroughly in research on social deficits and autism in FXS. This is of note, given the differences between males and females with FXS, with females exhibiting higher cognitive functioning in several domains compared with males (Freund and Reiss, 1991; Hagerman et al., 1992). As a group, males with FXS generally score within the moderate to severely intellectually disabled range (mean IQ around 50), while females demonstrate much greater variability in intellectual functioning, and on average function at a higher level (mean IQ around 75-80) than their male counterparts, with some displaying IQs in the normal range (Freund and Reiss, 1991; Reiss and Dant, 2003). Some data support a similar autistic profile in males and females with FXS, but in females the profile is less severe, translating to a lower frequency of ASD diagnoses among FXS females (Mazzocco et al., 1997). Full understanding of possible gender effects in FXS+ASD awaits direct comparison between males and females.

Given the argument for a continuum of autistic behavior in FXS, it is likely that among individuals with FXS there are individual differences related to the level of social interest, which underlies the behavioral symptoms of social awkwardness and anxiety. We propose that these individual differences may be related to differences in neural circuits involved in social cognition. For instance, previous neuroimaging findings on face processing in females with FXS report lack of the typical differentiation in activation to forward vs. angled faces in the fusiform gyrus (FG) and reduced left superior temporal sulcus (STS) activity, suggesting a neural basis for abnormal social perception (Garrett et al., 2004). Further, male premutation carriers demonstrate failure to activate social cognition regions such as the STS, orbitofrontal

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cortex, and insula in response to passive viewing of fearful faces (Hessl et al., 2007). Taken together, these data imply abnormal functioning of social cognition regions during basic processing of social stimuli in FXS and in male premutation carriers.

The FXS behavioral phenotype also includes memory deficits. Individuals with FXS exhibit poor performance during tasks probing working memory (Cornish et al., 2001; Munir et al., 2000) and visuospatial memory (Cornish et al., 1999; Crowe and Hay, 1990; Freund and Reiss, 1991). Findings related to short-term memory performance in FXS suggest that the ability to remember depends on what type of material is to be remembered (verbal, non-verbal) and on the context in which information is presented (concrete, abstract) (Maes et al., 1994; Munir et al., 2000). Individuals with FXS exhibit reduced neural activity in the hippocampal formation, a region heavily involved in memory, during encoding of visuospatial stimuli (Greicius et al., 2004) and during behavioral inhibition (Menon et al., 2004). Overall, individuals with FXS demonstrate deficits in memory, both at the behavioral and neural level.

Evidence exists to suggest that at least some of the variance in social deficits in individuals with idiopathic autism (IA) may be related to memory processes. Individuals with IA demonstrate impaired memory for faces (Blair et al., 2002; Boucher and Lewis, 1992; de Gelder et al., 1991; Gepner et al., 1996, Klin et al., 1999; Williams et al., 2005). Studies indicate a specific reduced ability to recognize previously seen unfamiliar faces (but not objects such as buildings) in those with IA compared to individuals with learning disabilities (matched on verbal and non-verbal mental age) and to typically developing individuals (matched on chronological age). Moreover, these deficits do not appear to be related to time spent looking at the faces or to visual memory deficits (Boucher and Lewis, 1992; Klin et al., 1999), although others suggest that the face recognition impairment may be part of a larger memory deficit (Williams et al., 2005). The underlying nature of this deficit remains to be identified, especially with regard to whether it is the social nature or visual complexity of faces that is related to face memory impairment in IA.

We propose that similar to individuals with IA, hyperarousal and increased anxiety in social situations in FXS may be related to memory processes, such as abnormal encoding of social cues and corresponding abnormal neural activity. As previously mentioned, individuals with FXS exhibit a wide range of memory deficits (Crowe and Hay, 1990; Freund and Reiss, 1991; Maes et al., 1994; Munir et al., 2000). Further, while few studies have examined memory functioning related to social cues in FXS, Cornish and colleagues reported that compared to a typically-developing group, individuals with FXS demonstrate (non-significantly) poorer performance on tasks probing memory for faces, although relationships between face memory performance and social anxiety behaviors were not examined (Cornish et al., 2001). To date, therefore, no studies have systematically examined whether social anxiety in FXS is related to processes beyond basic face perception, such as encoding of emotional faces. Our goals for this study were to identify potential differences in behavioral and neural patterns associated with memory for faces in individuals with FXS and typically-developing individuals and to establish whether neural mechanisms are related to behavioral measures of social anxiety in FXS.

The subsequent memory paradigm (Paller and Wagner, 2002) provides a unique opportunity to examine our research questions related to memory and social cognition. This paradigm involves sorting trials within an fMRI study according to behavioral performance on a memory test following the fMRI session (i.e., remembered vs. forgotten). Successful encoding of stimuli is assumed to be reflected in greater neural activity in the hippocampus and right prefrontal cortex during exposure to remembered items, compared to those that are forgotten (Brewer et al., 1998). This phenomenon is known as the Dm (difference in memory) effect. In typically-developing individuals, fMRI studies on face memory suggest that successful encoding of

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emotional faces is reflected in greater activation in the inferior frontal gyrus (IFG), ventrolateral prefrontal cortex (VLPFC), dorsolateral prefrontal cortex (DLPFC), parahippocampal gyrus (PHG), and FG compared to activation in response to non-encoded faces (Bernstein et al., 2002; Sergerie et al., 2005).

In the current investigation, we studied individuals with FXS and age- and gender-matched typically developing individuals who underwent scanning during a face encoding task, with online eye gaze tracking, after which they completed a recognition memory task and a social anxiety questionnaire. Trials during the fMRI face encoding task were then sorted according to the subsequent memory paradigm, and fMRI data analyzed to explore within- and between-group differences. We expected that compared to a control group, individuals with FXS would demonstrate a) reduced eyeand face-fixation; b) higher levels of social anxiety; and c) a robust Dm effect in non-socially relevant encoding regions but a reduced Dm effect in regions specifically associated with social cognition. Further, given the similarities in social deficits between FXS and IA, evidence of memory deficits in FXS, and previous findings of impaired face memory in IA, we predicted poorer behavioral performance in individuals with FXS on the memory task. Finally, we pursued several exploratory analyses. These included examination of the relationship between eye-fixation and memory for faces, and of the association between activation during successful face encoding and behavioral measures of social anxiety, such as level of eye-fixation and scores on a social anxiety questionnaire, as well as possible gender differences in the FXS group.

Materials and Methods

Subjects

Eleven individuals with full-mutation fragile X syndrome (6 F, 5 M; 10 right-handed; age: M = 18.5, SD = 4.1) were recruited for this study through a list of individuals who had previously participated in fMRI studies on FXS at the Waisman Center and through a listserv maintained by regional FXS resource groups associated with the National Fragile X Foundation. The diagnosis of FXS was confirmed through review of medical records that included genetic testing for FXS. All individuals met diagnostic criteria for full-mutation FXS. Seven individuals with FXS were medication-free. The remaining 4 participants with FXS were taking the following medications: (1) fluoxetine, methylphenidate; (2) fluoxetine; (3) fluoxetine, quetiapine; (4) clonidine, amantadine, carbamazepine. The FXS group was matched on age, gender, and handedness to a control group of 11 typically-developing individuals (6 F, 5 M; 10 right-handed; age: M = 18.7, SD = 5.8) who responded to local recruitment flyers. All control participants were medication free.

Cognitive functioning of all participants was assessed using the Wide-Range Intelligence Test (WRIT; Glutting et al., 2000). Autism characteristics in the FXS group were assessed using the Social Communication Questionnaire (SCQ) (Rutter et al., 2003). The SCQ is a 40-item, yes/no questionnaire completed by a parent or primary care provider that focuses on the child's developmental history with an emphasis on diagnostic features included in the more comprehensive Autism Diagnostic Interview - Revised (ADI-R) (Lord et al., 1994). Higher scores on the SCQ indicate greater endorsement of autistic characteristics, with a cut-off of 15 considered as indicative of a likely ASD. Data on the SCQ were missing for one female subject with FXS, and were not collected for the TD group.

Level of social anxiety in both the FXS and TD groups was assessed through completion of either the Social Phobia and Anxiety Inventory (SPAI; for individuals age 15 and older; Turner et al., 1996) or the Social Phobia and Anxiety Inventory for Children (SPAI-C; for individuals under the age of 15; Beidel et al., 1998). The SPAI is a 45-item questionnaire assessing anxiety in social situations and questions probing anxiety in non-social situations reflective of

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agoraphobia. The SPAI yields a Total Phobia score, Total Agoraphobia Score, and a Difference Score (Total Phobia - Total Agoraphobia). The Difference Score is used to determine likelihood of a Social Phobia diagnosis. The SPAI-C is a 26-item questionnaire probing anxiety in social situations in individuals age 8-14, phrased at an age-appropriate level. The SPAI-C yields a Total Social Phobia score and does not include questions on agoraphobia. The SPAI and SPAI-C specifically probe socially-related anxiety, not generalized anxiety or anxiety due to claustrophobia, thus can be considered a distinct measure of social anxiety in FXS separate from anxiety that may have been experienced in the MRI scanning environment. These measures have been used previously to measure social anxiety in individuals with FXS (Lesniak-Karpiak et al., 2003). For some individuals with FXS over the age 15, after consulting with the parent or legal guardian, it was determined that the SPAI-C would be more appropriate for assessment of social anxiety, as the items on the SPAI-C would more properly address these participants' mental age and functioning level. In order to standardize scores across these two measures (the SPAI and SPAI-C, each of which derive total scores through different algorithms), a z-score was obtained for each participant. For individuals who completed the SPAI, a z-score was calculated based on each individual's Difference Score. For individuals who completed the SPAI-C, a z-score was calculated based on each individual's Total Social Phobia score. Individuals with FXS on whom the SPAI was used had a mean mental age (MA) of 15.86, while the mean MA of those given the SPAI-C was 7.72. A complete SPAI questionnaire was not obtained for one individual in the FXS group. Three individuals with FXS completed the SPAI and/or SPAI-C with the assistance of a parent.

Procedure

All participants underwent thorough consent and assent procedures before commencing study procedures. Parent or legal guardian consent was obtained for all individuals under the age of 18. Separate adolescent consent was obtained for individuals aged 13-18, while child assent was obtained from participants aged 12 and younger. All participants were pre-screened for MRI compatibility before commencing MRI procedures.

For all participants with FXS and 3 control participants (those who were under the age of 18), sessions began with an MRI simulation session in a mock MRI that served as an introduction to MRI scanning procedures. These participants and their parents were allowed to explore the mock MRI and practice a modified version of the face encoding task (described below) during this session. In this modified version of the face encoding task, individuals practiced the task using unique stimuli (which were not repeated in the actual fMRI scanning session). Practice on this task allowed for the verification that participants, even those with lower IQ, were able to understand the instructions and perform the task. (Those control participants who did not undergo the mock scanning session did not practice the task. However, their performance on the task inside the scanner did not differ from those who had previous practice.) Once these participants reached an adequate level of comfort with the mock MRI and with MRI procedures, they were escorted to the real MRI for the actual scans. Scanning sessions began with 5-7 minutes of set-up and field-mapping scans, followed by functional and anatomical scanning (described below), for a total of 35-40 minutes. All participants were monetarily compensated for their participation.

Face Encoding Phase: Gender Discrimination Task

During the face encoding phase of the study, as part of the functional scanning session, participants completed a gender discrimination task. For this task, 10 female and 10 male faces displaying a fearful expression, obtained from the Karolinska Directed Emotional Faces set (Lundqvist et al., 1998; see Figure 1), were presented two times each in random order. Participants were instructed to make a gender discrimination and to press one of two buttons to indicate whether the face presented was male or female. In addition, participants were

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instructed to pay close attention to each stimulus, as they would be asked about the stimuli after the scanning session. All images of faces were of college-age individuals, cropped at the shoulders, 400 × 543 pixels, presented in full color on an 800 × 600 pixel black background and matched for luminance. Each face was presented for 3 sec, with a 5-7 second fixation screen between each face. Presentation of face stimuli was programmed and displayed using ePrime software, with acquisition of accuracy and reaction time during the task. Mean reaction time for each subject was calculated across all trials. Face stimuli were presented in the scanner with the Avotec Silent Vision system that includes automated eye tracking. Data on the gender discrimination task were not collected for 4 female individuals with FXS and 1 individual in the control group due to technical error. However, examination of eye-gaze data verified that these individuals were attending to visual stimuli. Therefore, the fMRI data for these individuals were included in group analyses.

Eye Movements

Eye movements, fixations and pupil diameter were acquired using an iView system with a remote eye-tracking device (SensoMotoric Instruments, 2001) and analyzed using iView software. This system tracks eye movement as the gaze position of the pupil over a certain length of time (gaze path) along with the amount of time spent on any given fixation point (gaze-fixation). Total fixation time for the eye region, mouth region, and face in general (including everything except for the defined eye and mouth regions) was calculated as the sum of fixations [each fixation defined as the amount of continuous time (minimum 50 ms) spent looking within each of these regions] within each of these three predefined regions for each face. The nose region was not defined as a separate region, but included in the overall face region. Our analytic methods for gaze-fixation data were based on previous studies on autism, which indicate that activity in face-processing regions such as the fusiform gyrus and amygdala is highly related to amount of eye- and face-fixation (Dalton et al., 2005).

Subsequent Memory Phase: Recognition Memory Task

Following the scanning session, participants were asked to perform a recognition memory task. The task began 30 minutes after the end of the gender discrimination task. During the period between the end of the gender discrimination task and the recognition memory task, participants completed the imaging procedures, left the imaging area, and rested quietly in a small room outside the scanning area. Participants viewed all images that had previously been presented during the scanning session as part of the gender discrimination task (20 target face stimuli) and an equivalent number of distractor images not previously viewed (20 distractor face stimuli). Participants were asked to verbally respond “yes” if they remembered viewing the face in the scanner and “no” if they did not remember viewing the face in scanner during the gender discrimination task. Presentation of face stimuli was programmed and displayed using ePrime software, with acquisition of accuracy and reaction time data during the task. Mean reaction time for each subject was calculated across all trials. Participants' overall memory performance was assessed based on principles of signal detection theory (Green and Swets, 1966). Specifically, for each subject, sensitivity (d') and response bias (ß) were calculated, based on raw number of hits and false alarms. Variables related to memory performance were also used to classify each gender discrimination task trial during the face encoding phase according to whether the subject did or did not remember the stimulus. Data for each stimulus were separated into subsequent memory categories based on response during the memory test: 1) stimuli that were remembered (successfully encoded faces), and 2) stimuli that were not remembered (unsuccessfully encoded faces). These groupings were then utilized as categories of interest (subsequent memory categories) in the fMRI GLM analysis (see below).

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Imaging

MRI data were acquired on a GE 3T scanner equipped with high-speed gradients and a whole-head transmit-receive quadrature birdcage headcoil (GE Medical Systems, Waukesha, WI). Functional data were obtained using a T2*-weighted gradient echo, echo planar sequence with sagittal acquisitions at a slice thickness of 4 mm (1 mm gap). We obtained 404 functional images for each participant (flip angle = 60°, TE = 30 ms, TR = 2000 ms, FOV = 240 × 240mm (64×64 matrix). High resolution anatomical scans, used to localize functional activation, were then obtained with a 3D T1 SPGR pulse sequence (TE = minimum, TR = 8.4 ms, FOV = 240 × 240, flip angle = 30°, NEX = 1, 256 × 192 matrix, 124 axial slices, slice thickness = 1-1.2mm).

Image Analysis

fMRI data were analyzed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Images were subjected to the following preprocessing steps: image reconstruction (during which the first 5 images of the run were discarded), removal of skull and ghost artifacts via a spatial Fermi filter, 6-parameter rigid-body motion correction, and slice-scan timing correction. Individual subject GLMs were modeled to estimate hemodynamic response for each subsequent memory category (successfully encoded and unsuccessfully encoded) with a sine variate that specified 5 sine functions spread over a 20-sec period following stimulus onset. Predictors based on each subject's estimated motion (3 for translation motion, 3 for rotation motion) were also built into each single-subject GLM to model possible variance due to motion (Johnstone et al., 2006). [The FXS group had mean motion parameters of 0.25 mm, 0.11 mm, 0.13 mm, 0.12 radians, 0.14 radians, and 0.22 radians for translation (x-plane, y-plane, z-plane) and rotation (pitch, roll and yaw) movement. For the TD group, these mean motion parameters values were 0.19 mm, 0.11 mm, 0.09 mm, 0.06 radians, 0.08 radians, and 0.15 radians. Groups differed significantly in amount of pitch rotation ($t(1,20) = 2.22$, $p = .038$), with the FXS group displaying a greater amount of rotation movement.] Resultant parameter estimates for both the entire 20-sec time-series (individual response function) and for an 8-sec range of the time-series corresponding to the likely peak in activation (2-10 seconds post-stimulus onset) were converted to percentage signal change. Percentage signal change maps from the GLM were spatially smoothed with a 4mm Gaussian kernel and transformed to Talairach space (Talairach and Tournoux, 1988) via identification of anatomical landmarks on the high-resolution T1 SPGR.

Group t-tests were executed in order to determine significant activation corresponding to the difference in memory (Dm) effect within and between the FXS and control groups, after accounting for variance associated with age and IQ. Specifically, these comparisons examined activation to the following subsequent memory categories: successfully encoded (subsequently remembered) versus unsuccessfully encoded (subsequently forgotten) faces. Clusters were detected following whole-brain Monte Carlo simulation in order to achieve a multiple-comparison corrected cluster threshold of $p<0.025$ and a minimum cluster size of 92. For clusters identified as significant, percentage signal change values for both the individual response function and 8-sec peak activation period were extracted for each subject and subsequent memory category and entered into SPSS 14 (SPSS, Inc., Chicago, IL) for further analysis of the source of the difference. For one individual in the control group, time-series data in one cluster detected in the between-group t-test met the criteria for outlier status (relative to the rest of the control group), based on the shape of this individual's time-series data, which did not conform to the hemodynamic response function. This outlier was excluded from further cluster analysis.

In addition to within-group and between-group analysis of brain activation maps, regression analyses were performed in order to identify neural regions in which brain activation in response to successfully encoded faces was predicted by eye-gaze fixation and (separately)

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level of social anxiety. Specifically, these analyses identified regions in which groups exhibited differences in the correlation between brain activation and a) eye-gaze fixation and b) level of social anxiety. For these between group analyses, eye-gaze fixation and level of social anxiety (SPAI z-score) were regressed separately (after accounting for variance associated with age and IQ) on whole-brain activation in response to successfully encoded faces. The resultant time-series were then modeled and extracted according to procedures described above. Within each group, correlations were computed between extracted percent signal change in regions surviving statistical threshold and behavioral data (eye-gaze fixation and SPAI z-score). These separate within-group correlations were then compared using Z value calculations to verify significant between-group differences in correlations.

Results

Group Characteristics

Individuals in the FXS group had a significantly lower mean IQ compared to the control group ($t(1,20) = 6.87$, $p = .001$) (see Table 1 for a summary of group characteristics). Reported social anxiety scores for the FXS group were significantly higher than the control group ($t(1,20) = 2.51$, $p = .021$). In the FXS group, SPAI z-score was significantly negatively correlated with IQ ($r = -.64$, $p = .045$); this relationship approached significance in the control group ($r = -.56$, $p = .074$). Individuals with FXS, as a group, exhibited a moderate level of autistic behaviors, with a mean SCQ score of 14.6. SCQ and SPAI z-scores were positively correlated in the FXS group ($r = .87$, $p = .002$).

Behavioral Performance on the Gender Discrimination Task

Individuals with FXS did not perform significantly differently on the gender discrimination task ($M = 82.9\%$ correct, $SD = 20.2$) compared to typically-developing controls [$M = 94.7\%$ correct, $SD = 7.8$; $t(1,15) = 1.70$, $p = .110$]. Individuals with FXS were similar to the control group in their ability to distinguish males and females, although they demonstrated greater variability in their performance. Additionally, the FXS group demonstrated similar reaction time in responding during the gender discrimination task ($M = 699.8$ ms, $SD = 551.5$) as the control group [$M = 686.1$ ms, $SD = 537.4$; $t(1,15) = 0.05$, $p = .96$], indicating that groups did not differ in the amount of time necessary to judge whether a stimulus face was male or female.

Behavioral Performance on the Recognition Memory Task

Performance on the recognition memory task was calculated based on principles of signal detection theory (Green and Swets, 1966). Specifically, for each subject, we calculated sensitivity (d') and response bias (ß) to faces for each subject, based on raw number of hits and false alarms. Individuals in the control group ($M = 1.89$, $SD = 1.07$) showed significantly higher sensitivity in their detection of target and distractor faces compared to the FXS group ($M = .62$, $SD = .81$; $t(1,20) = 3.15$, $p = .005$), suggesting that the control group was better able to judge correctly whether or not a target face had been previously viewed. In addition, the control group ($M = 1.10$, $SD = .79$) exhibited a significantly higher response bias than the FXS group ($M = .39$, $SD = .65$; $t(1,20) = 2.31$, $p = .032$), indicating that in situations in which it was uncertain whether the face had been viewed before, individuals in the control group were more likely to report that the target face had been previously viewed. Individuals with FXS remembered fewer previously viewed target faces ($M = 23.1$, $SD = 8.1$) than the control group ($M = 29.1$, $SD = 4.6$; $t(1,20) = 2.12$, $p = .046$).

Neither group showed a significant relationship between d' and SPAI z-score ($|r| = .19$-$.35$, n.s.). However, the FXS group demonstrated a significant negative relationship between SPAI z-score and ß ($r = -.65$, $p = .043$), suggesting that when they were unsure about whether they had or had not previously seen a face, those in the FXS group with higher levels of social

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anxiety were less likely to report that they had previously viewed the face. Further, in the FXS group, but not the control group, IQ was positively correlated with d' (r = .74, p = .010) and ß (r = .69, p = .018). Individuals with FXS who had higher IQ scores performed more accurately on the recognition memory task. Finally, the FXS group was slower than the control group in responding during the recognition task for both distractor faces [FXS: M = 3335.2 ms, SD = 1303.9; control: M = 2215.2 ms, SD = 386.4; t(1,20) = 2.73, p = .013] and target faces [FXS: M = 2864.7 ms, SD = 1047.9; control: M = 2137.8 ms, SD = 372.5; t(1,20) = 2.17; p = .042]. Individuals in the FXS group took longer than the control group to decide whether or not they had previously seen a stimulus face.

Gaze-fixation

The total amount of time spent fixating on the face, eyes, and mouth was calculated as the sum of fixations within each of these three predefined regions across target stimuli. The FXS group spent significantly less time looking at the eyes (t(1,20) = 2.93, p = .008) and face (t(1,20) = 2.44, p = .024) compared to the control group (see Figure 2). Neither group spent more time looking at the eyes, mouth, or face of subsequently remembered stimuli compared to subsequently forgotten stimuli (t = .09-.87, all n.s.), suggesting that successful memory for faces was not related to the amount of time looking at faces, and further that poorer memory performance in the FXS group was not due to reduced time spent looking at the face. Within each group, there were no correlations between eye, mouth or face fixation and IQ, d', or ß (|r| = .03-.55, all n.s.), suggesting that gaze-fixation was not related to cognitive functioning or performance on the recognition memory task in either group. Interestingly, in the control group there was a significant correlation between SPAI z-score and mouth fixation (r = .68, p = .020), and trends towards positive correlations between SPAI z-score and eye (r = .50, p = .120) and face (r = .57, p = .067) fixation. Correlations between eye, mouth, and face fixation and SPAI z-score were not significant in the FXS group (|r| = .03-.27, all n.s.). These findings could indicate that typically-developing individuals who have higher (but non-clinical) levels of social anxiety tend to spend more time looking at the eyes, mouth, and face than those with lower levels of social anxiety. Further, this suggests that social anxiety in FXS is not related to the amount of eye, mouth, or face fixation.

fMRI Data: Control Group Dm effect

Within the control group, the main effect of subsequent memory (activation to subsequently remembered minus subsequently forgotten stimuli - Dm effect) was compared across whole-brain. Individuals in the control group showed a pattern of neural activation associated with the Dm effect in regions involved in encoding and storage, including the right PHG and left IFG, and in regions related to social cognition, including the bilateral SFG and left medial frontal gyrus (MFG; see Table 2). The control group also showed neural activation associated with the Dm effect in the putamen and in posterior visual processing regions. Individuals in the control group exhibited greater activation in these regions during successful encoding of faces than during unsuccessful encoding of faces.

fMRI Data: FXS Group Dm effect

Similar to the control group, individuals with FXS demonstrated a Dm effect in the bilateral PHG and left IFG (see Table 3). Individuals with FXS also displayed activation associated with the Dm effect in the left amygdala, a region involved in emotional processing, as well as face processing regions including the bilateral FG. The FXS group also showed Dm effect activation in the left insula, left posterior cingulate gyrus, and bilateral cerebellum. Individuals in the FXS group recruited these regions during successful encoding of faces to a greater degree than during unsuccessful encoding of faces. However, the FXS group failed to show significant

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levels of activation associated with the Dm effect in social cognition regions including the SFG and MFG.

fMRI Data: Control vs. FXS Dm effect

In order to assess between-group differences in neural patterns associated with subsequent memory for faces, activation maps for the Dm effect for the FXS and control groups were compared directly. The control group showed a greater Dm effect compared to the FXS group in the left SFG and left MFG (see Table 4 and Figure 3). Further visual examination of the averaged MR time series for the Dm effect in each group reveals robust SFG and MFG activation in the control group in response to subsequently remembered but not subsequently forgotten faces, whereas the FXS group exhibited decreased activation in the SFG and MFG in response to both subsequently remembered and subsequently forgotten faces (see Figure 3).

Group Differences in Correlations between Brain Activation and Gaze-Fixation

Given the high degree of variability in eye-gaze among participants in each group, a regression analysis was carried out in order to examine whether eye-gaze predicted activation in response to successfully encoded faces differently between groups, in a voxel-wise fashion after accounting for variance associated with age and IQ. Neural activation in response to faces that were later remembered was positively correlated with the amount of time spent looking at the eyes for the FXS group but not in the control group in the left angular gyrus (see Table 5 and Figure 4). Individuals with FXS who displayed higher levels of eye fixation showed greater activation in the left angular gyrus during successful encoding of faces. Conversely, neural activation in response to faces that were later remembered was positively correlated with the amount of time spent looking at the eyes for the control group and non-significantly negatively correlated with the amount of time spent looking at the eyes in the FXS group in the left insula (see Table 5 and Figure 4). Finally, neural activation in response to faces that were later remembered was positively correlated with the amount of time spent looking at the eyes for the control group and negatively correlated with the amount of time spent looking at the eyes in the FXS group in the left posterior cingulate gyrus. Independent of age and cognitive functioning level, individuals with FXS who demonstrated higher levels of eye fixation showed less activation in the posterior cingulate gyrus during successful encoding of faces, while those in the control group showed a positive relationship, with higher eye fixation associated with greater activation in the posterior cingulate gyrus and insula.

Group Differences in Correlations between Brain Activation and Social Anxiety

While FXS and control groups differed significantly on SPAI z-scores, social anxiety levels in both groups were highly variable. We took advantage of this variability by carrying out an additional regression analysis in order to determine whether brain activation associated with successful encoding was related to the level of social anxiety differently between groups. For this analysis, SPAI z-scores in the each group were regressed on neural activation in response to successfully encoded faces in a voxel-wise fashion after accounting for variance associated with age and IQ. This analysis revealed that brain activation in response to faces that were later remembered was negatively associated with SPAI z-score in the FXS group and positively associated with SPAI z-score in the control group in the left IFG and right MFG (see Table 6 and Figure 5). Finally, brain activation in response to faces that were later remembered was negatively associated with SPAI z-score in the FXS group but not related to SPAI z-score in the control group in the right SFG and left hippocampus. In the FXS group, individuals with higher levels of social anxiety exhibited lower activation in the left IFG, right MFG, right SFG, and left hippocampus during successful encoding of faces. Conversely, control participants with higher levels of social anxiety tended to show greater activation in the left IFG and right MFG while successfully encoding faces.

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Gender Effects: FXS Group

Given the diverging phenotypes between males and females with FXS, we examined whether these differences extended to behavioral and fMRI data for the current study. Compared to females, males with FXS exhibited lower IQ scores [males: M = 39.8, SD = 7.3; females: M = 81.7, SD = 15.8; t(1,9) = 5.44, p = .001] and higher SPAI z-scores [males: M = 1.2, SD = .83; females: M = -.09, SD = .61; t(1,9) = 2.78, p = .024] and SCQ scores [males: M = 22.4, SD = 8.3; females: M = 6.8, SD = 2.2; t(1,8) = 4.54, p = .004]. However, males and females with FXS did not differ significantly in age, d', ß, or eye, face, or mouth fixation. Further, males and females displayed similar levels of activation associated with the Dm effect in regions of interest identified as part of the FXS group Dm effect analysis and ROIs identified as part of the FXS vs. control group analysis. Beyond expected differences in IQ level and degree of social anxiety, males and females with FXS do not appear to demonstrate significant differences in gaze fixation or face encoding, both at the behavioral and neural level.

Discussion

This study examined the interaction between emotional face processing and memory as related to social anxiety in individuals with fragile X syndrome compared to typically-developing individuals. At the behavioral level, individuals with FXS demonstrated poorer ability to distinguish previously viewed faces compared to typically-developing individuals (i.e., poorer memory for faces), although this group difference was largely an effect of lower cognitive functioning. Further, gaze-fixation results provide evidence that although individuals with FXS showed significantly lower eye- and face-fixation compared to the control group, successful encoding of faces was not related to the amount of time spent looking at the eyes or face in either group. We speculate that if the encoding task had involved emotion (rather than gender) discrimination, these gaze-fixation results might have been different. In fact, data exist to suggest abnormal fusiform gyrus activation related to gaze-fixation patterns during an emotion discrimination task in individuals with FXS (Dalton et al., in press), which indicates the possibility of distinct, task-dependent relationships between gaze-fixation and brain activation associated with face processing in FXS.

Our neuroimaging results revealed unique patterns of neural activation during face encoding in individuals with FXS, who showed highly contrasting relationships between brain activation and both gaze-fixation and social anxiety levels compared to typically-developing individuals. The control group demonstrated a stronger Dm effect than the FXS group in frontal regions associated with social cognition (SFG and MFG). Additionally, in the FXS group, eye-fixation was negatively associated with activation to subsequently remembered faces in regions involved in both attention (posterior cingulate gyrus) and orienting to emotional cues (insula), and positively related to activation in multisensory association regions (angular gyrus), patterns opposite of those seen in the control group. Finally, regression analyses demonstrated that individuals with FXS who have higher levels of social anxiety showed less activation in response to faces that they later remembered in frontal social cognition regions and in hippocampal memory areas, while reverse relationships were seen in the control group. We believe that our neuroimaging findings, which show dysfunction in several specialized neural networks, support the theory that neural functioning abnormalities in FXS derive from the interaction between genetic and neural processes throughout the brain that compound over time, leading to network-wide dysfunction (Belmonte and Bourgeron, 2006).

As expected, both FXS and control groups demonstrated a robust Dm effect in the PHG and IFG, regions well-established as part of the successful encoding network (Paller and Wagner, 2002). This across-group finding suggests that individuals with FXS were similar to typically-developing individuals in their ability to recruit networks involved in successful encoding. However, direct group contrast of Dm effect activation indicated that individuals in the control

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group exhibited a stronger Dm effect than the FXS group in the SFG and MFG, regions that fall within the boundaries of the ventrolateral prefrontal cortex (VLPFC). The VLPFC plays unique roles in both memory processes (updating and maintaining contents of working memory; for a review, see Fletcher and Henson, 2001) and social cognition (controlled processes associated with awareness, intention, and effort; Wegner and Bargh, 1998). In particular, the VLPFC is involved in tasks probing autobiographical and episodic memory (Gilboa, 2004), judgment of another person's actions (Mason et al., 2004), inhibiting the self-experience while considering another's perspective (Baron-Cohen et al., 1999; Vogeley et al., 2001), and recognition of self vs. others (Platek et al., 2006; Uddin et al., 2005). In addition, previous neuroimaging reports cite activation in prefrontal areas within or just medial to the current SFG and MFG regions during various types of face encoding tasks, including basic face encoding (Haxby et al., 1996) and those that require subjects to form impressions of the individuals presented (Mitchell et al., 2004) and judge the pleasantness of the face (Bernstein et al., 2002). Moreover, medial prefrontal cortex (MPFC) activation has been shown to predict successful encoding of pictures with social content, as compared to non-social images, suggesting that MPFC is involved in self-referential processes which aid in the formation of socially-relevant memories (Harvey et al., 2007). As such, this pattern of activation in the control group suggests that successful encoding of faces in typically-developing individuals involves engagement of social cognition networks.

Interestingly, individuals with FXS not only failed to recruit these regions, they demonstrated decreased activation in the SFG and MFG in response to successfully encoded faces. This pattern of response is difficult to interpret. However, individuals with full mutation FXS have previously been found to exhibit decreased activation compared to typically-developing individuals in the SFG during arithmetic processing (Rivera et al., 2002). Reduced VLPFC activation in response to a go/nogo task was recently reported in a group of males with FXS, similar to our VLPFC results (but in the contralateral (right) hemisphere; Hoeft et al., 2007). These results, combined with findings of significant relationships between VLPFC and FMRP level (Hoeft et al., 2007; Menon et al., 2004), suggest this region may be consistently affected in FXS. In addition, recent findings suggest that male premutation carriers exhibit decreased activation in social cognition regions (such as the orbitofrontal cortex and superior temporal sulcus) during fearful face processing (Hessl et al., 2007).

We did not find differential group activation of the amygdala in response to the Dm effect. While the FXS group showed a Dm effect in the amygdala, direct group comparison failed to identify this region as significantly more responsive to the Dm effect in the FXS group compared to the control group. The amygdala is heavily involved in the consolidation of emotional information (Kensington and Schacter, 2006; for a review, see LaBar and Cabeza, 2006; Phelps, 2006) and in the successful encoding of unfamiliar faces (Bernstein et al., 2002; Dubois et al., 1999; Sergerie et al., 2006). Coupled activation of the amygdala and hippocampus in particular has been implicated in encoding and retrieval of emotional information (Dolcos et al., 2004; Erk et al., 2005; Richardson et al., 2004; Smith et al., 2006). However, evidence from a recent study implies that amygdala activation specifically predicts successful encoding of emotional (vs. neutral) pictures, but is not involved in encoding related to the social nature of pictures (Harvey et al., 2007). The lack of amygdala activation in response to the Dm effect the control group (and in the between-group comparison) in the current study may be due to the fact that individuals in the control group did not find the faces to be sufficiently emotional in nature. Consideration of previous findings and of the fact that we did not include a neutral face category may partially explain our findings (or lack thereof) in the amygdala.

Beyond this main set of group differences in the Dm effect, neural activity associated with successful encoding of faces was found to be related to the amount of time spent fixating the

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eyes, although the direction of this association differed between groups. Specifically, typically-developing individuals with greater eye fixation exhibited greater activity in the left insula and left posterior cingulate gyrus, while the opposite relationship held for the FXS group. Activity in these regions likely reflects neural substrates of attention and orientation to emotional expression, which, for the control group, appears to relate to the amount of time one spends looking at the eyes. In the FXS group, lower levels of activation in these regions for individuals who show increased eye fixation may be associated with phenomenological differences in the underlying neural mechanisms of gaze-fixation, which have been documented in this population (Dalton et al., 2006; Garrett et al., 2004). Individuals with FXS have previously been found to exhibit decreased activation compared to typically-developing individuals in the left insula during tasks involving processing of direct- vs. angled-gaze faces (Garrett et al., 2004) and cognitive interference (Tamm et al., 2002). In addition, these findings may add support to recent evidence suggesting that gaze avoidance in FXS is possibly more related to multisensory and task demand avoidance than to social anxiety per se (Murphy et al., 2007). Finally, individuals with FXS show a positive relationship between eye fixation and brain activation in the angular gyrus during face encoding. This relationship may be related to deficits in attention and multisensory integration as well as underlying molecular mechanisms, given that activation during a behavioral inhibition task in the left angular gyrus has previously been reported to be positively associated with FMRP expression in individuals with FXS (Menon et al., 2004; Rivera et al., 2002).

Neural dysfunction associated with social-emotional processing in FXS has been previously documented (Dalton et al., 2006; Garrett et al., 2004). However, one of the main goals of the present study was to take the investigation of neural mechanisms of phenotypic behaviors in FXS one step further by identifying neural substrates more closely associated social anxiety in FXS. Results of the regression of social anxiety level on brain activation in response to successfully encoded faces indicate contrasting relationships between neural function and social anxiety in individuals with FXS compared to typically-developing individuals. The FXS group demonstrated a negative association between social anxiety and activation in the SFG, MFG, and IFG, while the control group exhibited positive relationships between activity in these regions and level of social anxiety, differences that cannot be attributed to varying cognitive functioning between groups. These data suggest that individuals with FXS who have high social anxiety fail to recruit networks associated with successful encoding and social cognition, while those with lower levels of social anxiety engage these regions to a certain degree. The positive relationship seen in the control group indicates phenomenological differences between these groups in underlying mechanisms of social anxiety. It is possible that in control subjects, heightened activation in social cognition and encoding networks is suggestive of heightened arousal related to social information processing, perhaps in attempts to override anxiety.

Individuals with FXS also showed a negative relationship between activation in the hippocampus and social anxiety, such that individuals with the highest levels of social anxiety were least able to recruit this important memory-associated region during face encoding. The hippocampus in FXS is abnormal both at the gross anatomical level (enlarged; Kates et al., 1997; Reiss et al., 1994) and at the functional level (decreased activation compared to controls; Menon et al., 2004; Greicius et al., 2004). Importantly, the hippocampus is one of the regions of the brain with the greatest expression of FMRP (Abitbol et al., 1993; Hinds et al., 1993). In FXS, FMRP is positively related to activation in the hippocampus during behavioral inhibition (Menon et al., 2004). In light of these extant data, current findings suggest that hippocampal dysfunction in FXS extends to the interaction between behavioral symptoms of social anxiety and encoding of social information.

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It is striking that most of these regression results trend in the direction of negative relationships between brain activity and behavioral measures in the FXS group, except for the finding of a positive relationship between angular gyrus activation and eye fixation. We hypothesize that this relationship represents the confluence of molecular and neural mechanisms in a region uniquely involved in eye fixation. The angular gyrus represents the only one among these regions (i.e., those demonstrating relationships between brain activity and behavioral measures) that is not consistently involved in social/emotional processing. The angular gyrus, in addition to playing a role in reading and language (Humphries et al., 2007; Phinney et al., 2007) and math processing (Grabner et al., 2007), has also been shown to be involved in multisensory integration, specifically in non-voluntary (i.e., reflexive) visual field examination (Mort et al., 2003). Given the social and emotional deficits involved in the FXS phenotype, it is therefore not surprising that this region might demonstrate a somewhat different pattern, one in which increased activation during visual exploration of faces is directly and positively related to the amount of eye fixation. This trend may represent compensatory involvement of a region strictly involved in sensory processing. In addition, unlike the posterior cingulate and left insula, studies consistently report a positive relationship between angular gyrus activation (during both arithmetic processing and behavioral inhibition tasks) and FMRP expression (Menon et al., 2004; Rivera et al., 2002). Thus, while the control group demonstrated a positive relationship between eye fixation and activation in the insula and posterior cingulate, two regions involved in emotional processing, the FXS group, hampered by an inability to correctly recruit these regions during the task, may have relied on the angular gyrus for visual field examination of faces. Taken together, this suggests possible compensatory participation of the angular gyrus related to eye gaze fixation in individuals with FXS, which might relate to FMRP expression (though this latter idea remains untested and speculative).

Although the current data advance the understanding of social anxiety in FXS, several limitations to this study should be acknowledged, especially with respect to generalizability of our findings. First, the sample size was small, limiting our power to detect meaningful results. Thus, these findings should be considered preliminary. Additionally, we included a mixed group of individuals with FXS, with almost equal numbers of males and females. While males and females in this study showed differences in IQ and social anxiety level, they did not differ significantly in their level of gaze fixation or face encoding, either behaviorally or in their neural response associated with the Dm effect. The literature on FXS has documented phenotypic differences between males and females with FXS, and our inclusion of both genders may limit our ability to generalize to the FXS population as a whole. However, this study represents only the second fMRI study to include a large group of males with FXS who have lower cognitive functioning, a portion of the FXS population that has yet to be extensively studied.

Another limitation of the study was the wide age range across groups and significant group difference in IQ. Although we controlled for these factors in our analyses, a more valid approach would have been to narrow the age range and to include a group of individuals with developmental disabilities matched on chronological and mental age, in addition to the typically-developing control group. In addition, we did not include a comparison group of individuals with autism, who demonstrate similar heightened social anxiety level and deficits in face memory as individuals with FXS. Inclusion of these groups would have allowed for more meaningful conclusions regarding the role of cognitive ability and etiology of autistic behaviors (respectively) in the delineation of neural mechanisms of social anxiety in FXS. Further, we did not collect SCQ data for the TD group. Although we did not suspect any of the individuals in this group of meeting criteria for an autism spectrum disorder, nor did we observe any autism behaviors in these individuals, we cannot definitively rule out the possibility of the presence of autism characteristics in this group. Additionally, one of our FXS participants was taking methylphenidate at the time of the study. While this medication is

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known to affect frontal cortex function, within and between group results did not change significantly when this subject was excluded from analysis (data not shown). Finally, facial expression of the target stimuli was not varied. Such a design would have allowed for investigation of whether current findings are specific to fearful expressions or might be different (especially in the amygdala) according to the type and degree of emotion shown.

In conclusion, individuals with FXS were found to exhibit less activation in social cognition regions during successful vs. unsuccessful face encoding, compared to typically-developing individuals. Additional diverging results between groups were revealed in the relationships between activation in social cognition areas and behavioral measures of social anxiety, suggesting that social anxiety in FXS is likely related to the inability to recruit higher-level regions associated with processing of social information during the initial phases of memory formation. Future studies should utilize larger samples of individuals with FXS, systematically examine possible gender differences in FXS, and include comparison groups of individuals with IA and those matched on IQ.

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Figure 1.
Representative images of face stimuli.

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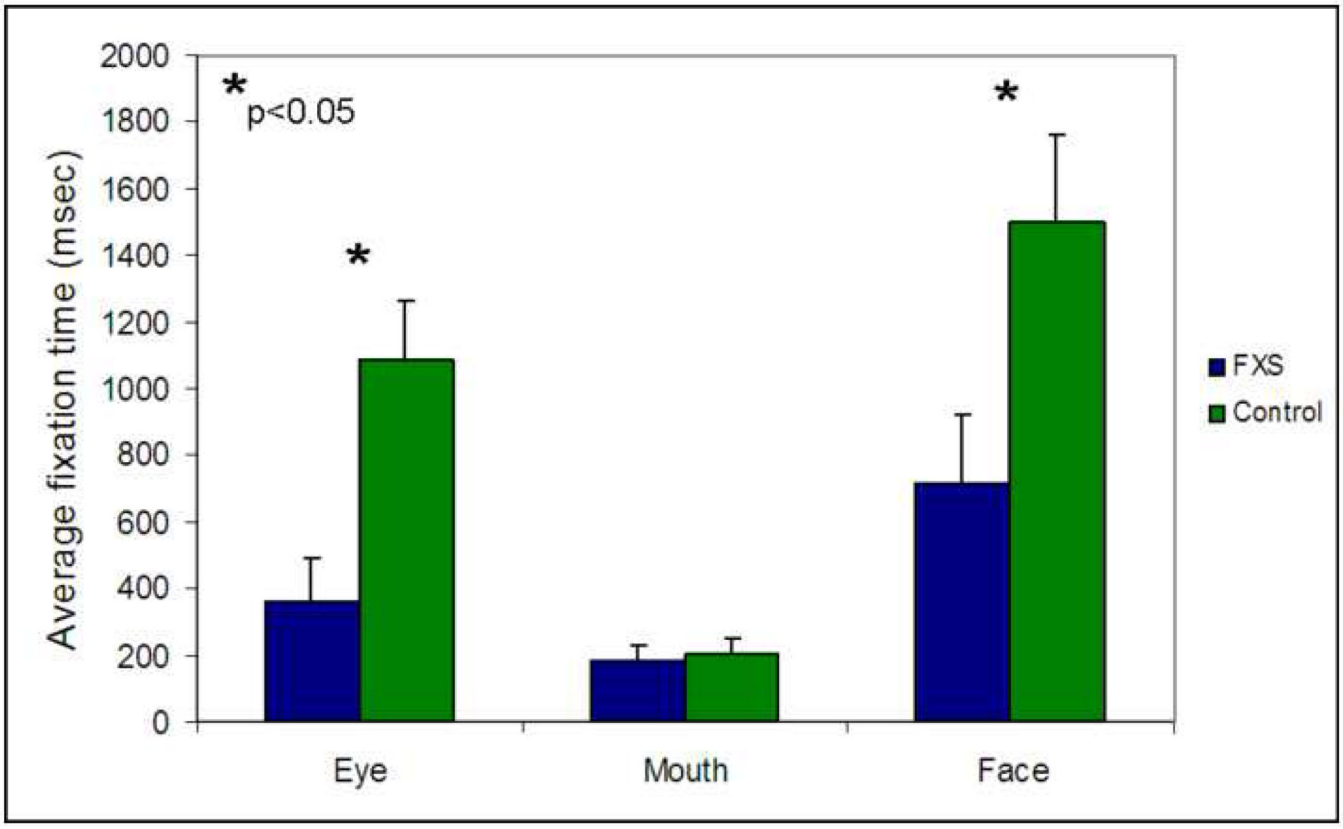

Figure 2.
Average fixation duration for eye, mouth, and face fixation by group. Error bars indicate the standard error of the mean.

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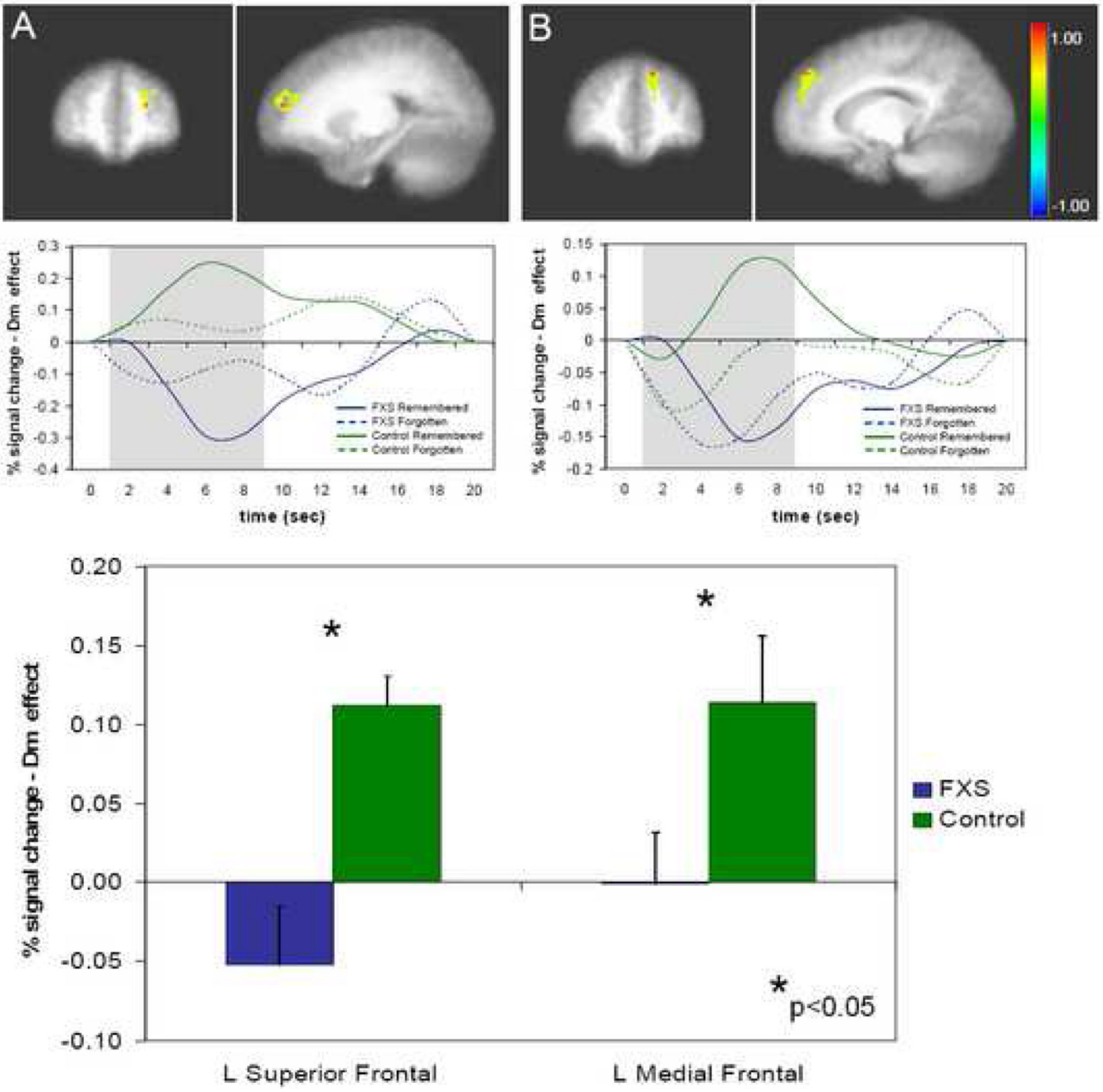

Figure 3.

Regions of interest in the FXS vs. control comparison of the Dm effect in which the control group showed greater activation than the FXS group (after accounting for variance associated with age and IQ). A: Left Superior Frontal gyrus (BA 10; -20,48,15), B: Left Medial Frontal gyrus (BA 8; -11,45,38) (images presented according to radiological convention, in which the right hemisphere is depicted on the left side of the coronal image). Averaged MR time series are presented below for each region for the 20 seconds following stimulus onset: FXS group - subsequently remembered (blue solid line), FXS group - subsequently forgotten (blue dashed line), Control group - subsequently remembered (green solid line), Control group - subsequently forgotten (green dashed line). Shaded portion of averaged time series indicates

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the section of the time series for which the percent signal change (for the Dm effect: subsequently remembered - subsequently forgotten) was extracted for graphing below.

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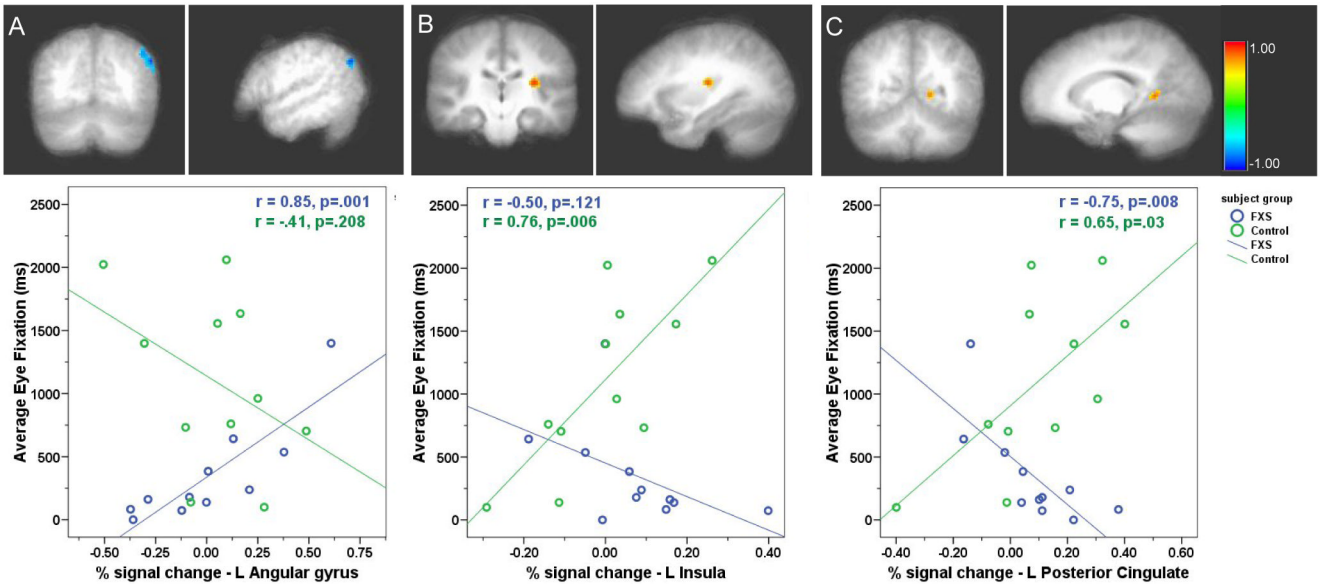

Figure 4.

Regions of interest in the regression of eye fixation duration on brain activation in response to successfully remembered faces in the FXS and control groups (after accounting for variance associated with age and IQ). A: Left Angular gyrus [-51,-65,36; Vol(mm^3)=1000], B: Left Insula [-29,-19,18; Vol(mm^3)=672], C: Left Posterior Cingulate gyrus [-15,-51,6; Vol(mm^3) =880] (images presented according to radiological convention, in which the right hemisphere is depicted on the left side of the coronal image). Scatterplots of the correlations between eye fixation duration and percent signal change in each region are shown below.

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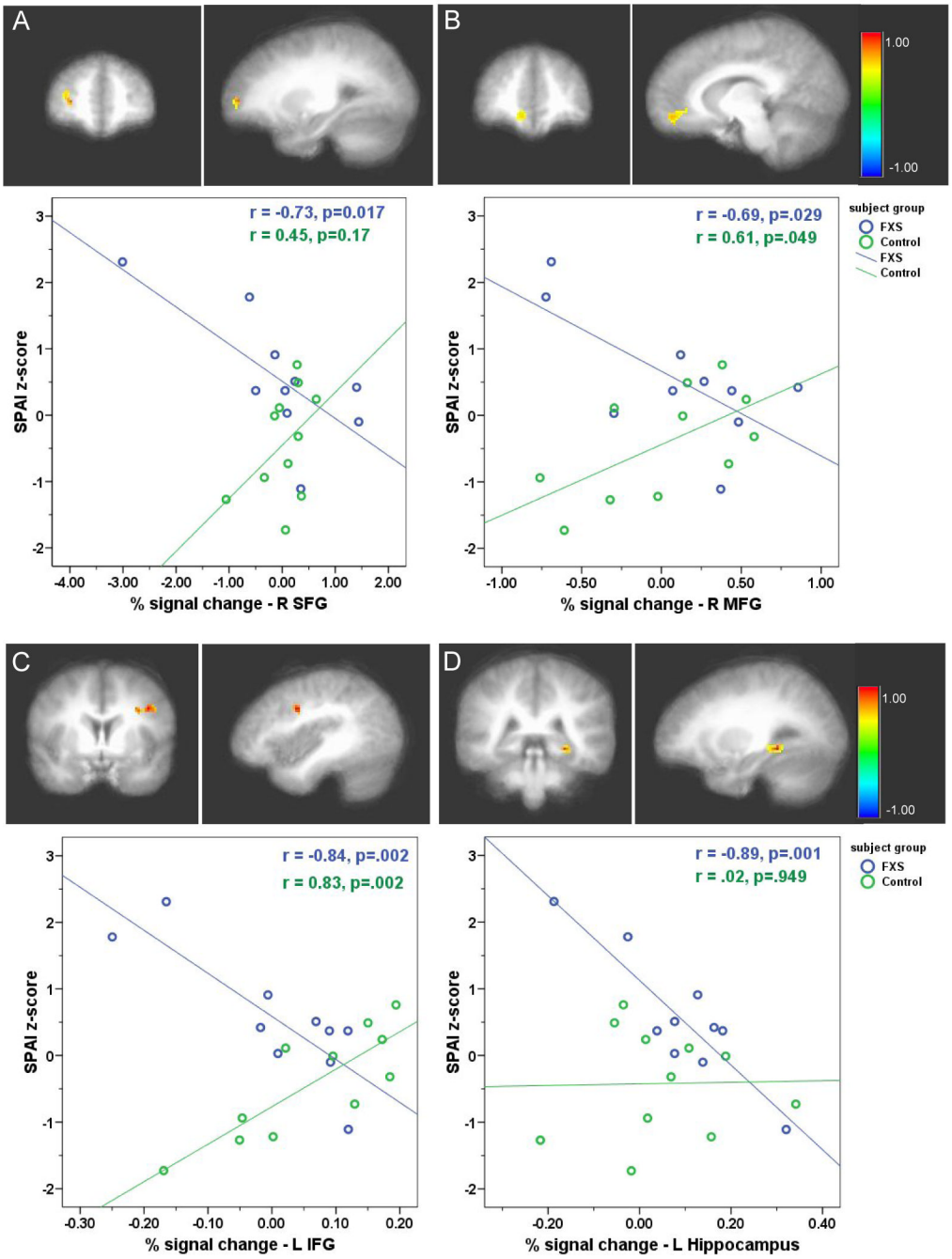

Figure 5.

Regions of interest in the regression of SPAI z-score on brain activation in response to successfully remembered faces in the FXS and control groups (after accounting for variance associated with age and IQ). A: Right Superior Frontal gyrus (25,51,6), B: Right Medial Frontal gyrus (11,47,-8), C: Left Inferior Frontal gyrus (-39,1,32), D: Left Hippocampus (-27,-39,-2) (images presented according to radiological convention, in which the right hemisphere is depicted on the left side of the coronal image). Scatterplots of the correlations between SPAI z-score and percent signal change in each region are shown below.

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Table 1

Group characteristics (n = 11/group)

	Group	
	FXSM (SD)	**Control M (SD)**
Age (yrs)	18.5 (4.1)	18.7 (5.8)
IQ	62.6 (25.0)	120.9 (13.0)
SPAI z-score	0.55 (0.96)	-0.42 (0.81)
SCQ	14.6 (10.0)	N/A

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Table 2

Significant activations associated with the subsequent memory (Dm) effect for faces (remembered versus forgotten faces) in the control group.

Region	Brodmann Area	Vol (mm^3)	Coordinates			t
			x	y	z	
R Parahippocampal gyrus	35	336	21	-35	-6	4.51
L Inferior Frontal gyrus	45	5136	-51	33	6	8.16
R Superior Frontal gyrus	8	840	15	41	40	8.50
L Superior Frontal gyrus	10	424	-20	48	15	8.18
L Medial Frontal gyrus	8	3864	-11	45	38	8.31
L Putamen	--	168	-23	-12	7	4.22
R Precuneus	19	816	37	-67	42	4.34
R Middle Occipital gyrus	19	4176	27	-87	12	8.14
R Lingual gyrus	30	4736	23	-53	0	5.35
L Lingual gyrus	17	6352	-17	-83	2	8.95

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Table 3

Significant activations associated with the subsequent memory (Dm) effect for faces (remembered versus forgotten faces) in the FXS group.

Region	Brodmann Area	Vol (mm^3)	Coordinates			t
			x	y	z	
R Parahippocampal gyrus	28	328	25	-19	-18	4.94
L Parahippocampal gyrus	36	192	-35	-31	-16	4.47
L Inferior Frontal gyrus	13	848	-41	27	12	11.93
L Inferior Frontal gyrus	47	1248	-27	13	-14	5.99
L Amygdala	--	144	-18	-9	-11	3.42
R Fusiform gyrus	37	1984	38	-47	-10	4.24
L Fusiform gyrus	20	112	-37	-41	-20	4.85
L Insula	13	920	-45	-21	16	6.04
L Posterior Cingulate gyrus	30	5552	-5	-63	14	7.48
R Cerebellum	--	760	13	-79	-14	6.13
L Cerebellum	--	2528	-37	-41	-20	4.85
L Cerebellum	--	1144	-5	-77	-14	5.46

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Table 4

Significant activations associated with the subsequent memory (Dm) effect for faces (remembered versus forgotten faces) in the control group vs. FXS group contrast.

Region	Brodmann Area	Vol (mm^3)	Coordinates			t
Control > FXS			x	y	z	
L Superior Frontal gyrus	10	424	-20	48	15	3.21
L Medial Frontal gyrus	8	3864	-11	45	38	3.30

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Table 5

Significant correlations between gaze-fixation and brain activation associated with the subsequent memory (Dm) effect for faces (remembered versus forgotten faces) in the control group and FXS group, and statistical comparison of between within-group correlations.

Region	Brodmann Area	Vol (mm^3)	Coordinates			r(p)		Z (1,20) (p)
FXS			x	y	z	FXS	Control	
L Angular gyrus	39	1000	-51	-65	36	0.85 (.001)	-0.41 (.208)	3.40 (.001)
L Insula	--	672	-29	19	18	-0.50 (.008)	0.76 (.006)	3.09 (.001)
L Posterior Cingulate gyrus	30	880	-15	-51	6	-0.75 (.008)	0.65 (.030)	3.50 (.001)

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Table 6

Significant correlations between SPAI z-score and brain activation associated with the subsequent memory (Dm) effect for faces (remembered versus forgotten faces) in the control group and FXS group, and statistical comparison of between within-group correlations.

Region	Brodmann Area	Vol (mm^3)	Coordinates			r(p)		Z (1,20) (p)
FXS			x	y	z	FXS	Control	
L Inferior Frontal gyrus	44	2504	-39	1	32	-0.84 (.002)	0.83 (.002)	4.63 (.001)
R Medial Frontal gyrus	10	776	11	47	-8	-0.69 (.029)	0.61 (.049)	2.98 (.002)
R Superior Frontal gyrus	10	872	25	51	6	-0.73 (.017)	0.45 (.17)	2.77 (.003)
L Hippocampus	--	736	-27	-39	-2	-0.89 (.000)	0.02 (.95)	2.82 (.002)