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Aberrant Neural Function During Emotion Attribution in Female Subjects With Fragile X Syndrome

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Abstract

Objective—Fragile X (FraX) syndrome is caused by mutations of the FraX mental retardation–1 gene—a gene responsible for producing FraX mental retardation protein. The neurocognitive phenotype associated with FraX in female subjects includes increased risk for emotional disorders including social anxiety, depression, and attention deficit. Here, the authors investigated the neurobiological systems underlying emotion attribution in female subjects with FraX syndrome.

Method—While undergoing functional magnetic resonance imaging, 10 high-functioning female subjects with FraX syndrome and 10 typically developing (TD) female subjects were presented with photographs of happy, sad, and neutral faces and instructed to determine the facial emotion.

Results—No significant group differences were found for the recognition of happy faces, although the FraX group showed a trend toward a significant difference for the recognition of sad faces and significantly poorer recognition of neutral faces. Controlling for between-group differences in IQ and performance accuracy, the TD group had greater activation than the FraX group in the anterior cingulate cortex (ACC) for neutral faces compared with scrambled faces and the caudate for sad faces compared with scrambled faces (but not for sad faces compared with neutral faces). In the FraX group, FraX mental retardation protein levels positively correlated with activation in the dorsal ACC for neutral, happy, and sad faces when independently compared with scrambled faces. Significantly greater negative correlation between IQ and insula activation for neutral faces relative to scrambled faces was observed in the FraX group compared with the TD

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group. Significantly greater positive correlation between IQ and ACC activation for neutral faces relative to scrambled faces was observed in the TD group compared with the FraX group.

Conclusions—Although emotion recognition is generally spared in FraX syndrome, the emotion circuit (i.e., ACC, caudate, insula) that modulates emotional responses to facial stimuli may be disrupted.

Keywords

fMRI; fragile X; emotion; cingulate cortex; insula

Fragile X (FraX) syndrome is the most common inherited form of brain dysfunction currently known. Fragile X syndrome results from anomalous expression of the FraX mental retardation–1 (*FMR1*) gene and is characterized by a repeating expansion of CGG nucleotides on the long arm of the X chromosome. The excessive CGG nucleotide repeats, and consequential hypermethylation of cytosines, extinguishes transcription of the *FMR1* gene and resultant translation of FraX mental retardation protein (FMRP). Suboptimal FMRP production is associated with abnormal brain development and function in affected people and animal knockout (KO) models of the disorder.[1–4] The severity of brain dysfunction and resulting cognitive and behavioral impairment varies across people with FraX and may partly be related to reduced FMRP production. The amount of FMRP produced and severity of cognitive and behavioral characteristics are more variable in females with the FraX full mutation than in males with the FraX full mutation.[4,5] Females with FraX syndrome therefore present an ideal group for studying the effects of FMRP on cognition and behavior.

Social anxiety has been shown to negatively correlate with FMRP levels in female subjects with FraX,[4] whereas behavioral problems positively correlate with levels of the stress hormone cortisol.[6] The typical neuropsychological profile of female subjects with FraX includes mild to moderate learning disabilities, social dysfunction, and problems with emotion regulation. Cognitive deficits may include, but are not limited to, impairments in executive functioning, arithmetic processing, and visuospatial ability.[4,7–10] With respect to socioemotional phenotype, female subjects with FraX typically exhibit greater levels of anxiety, social avoidance, and withdrawal in social situations.[4,11,12] Female subjects with FraX syndrome may be more prone to develop depression,[13] although it is unclear whether depression is a primary phenotypic feature of the disorder or a secondary feature resulting from social isolation or rejection by peers. Female subjects with FraX syndrome often reveal behaviors similar in quality to people with autism spectrum disorder, including difficulties with social relations and communication and diminished eye contact.[5]

A recent functional magnetic resonance imaging (MRI) study from our group showed adolescent female subjects with FraX to exhibit anomalous activity in the fusiform gyrus and superior temporal sulcus, two core face-processing regions[14–16] associated with the "social brain,"[17] during assessment of eye gaze.[18] *FMR1* KO mice show deficient amygdala functioning,[19,20] whereas human imaging studies of FraX show morphological differences, presumably arising from abnormal dendritic branching and synaptic pruning,[1–4] in the amygdala and other regions associated with emotion processing, including the caudate and

superior temporal gyrus.[3,4,15,16,21–24] Yet behavioral studies suggest that emotion recognition deficits in FraX may be related to intellectual level and/or the presence of autistic behaviors, rather than a pathognomonic characteristic of FraX.[11,25,26] However, two of these studies were limited to FraX male subjects[25,26] who have significant cognitive disability—this may have hindered the ability to detect group-specific effects. The one study of female subjects with FraX found that full-scale IQ (FSIQ) predicted performance on complex, but not basic, emotion recognition.[11]

Given the presence of emotion regulation difficulties in female subjects with FraX and the interesting behavioral associations between FraX and autism spectrum disorder,[27–29] we undertook the present study to elucidate the neural architecture underlying emotion attribution in FraX. Based on previous imaging and behavioral studies,[1–4,11,21,25,28] we hypothesized that, compared with the typically developing (TD) group, female subjects with FraX would exhibit abnormal activity in the neural systems modulating cortical-subcortical regulation of emotion (e.g., anterior cingulate cortex [ACC], caudate), as well as subcortical regions associated with affect processing (e.g., amygdala). To examine these regions, we used facial emotion stimuli, including sad and happy faces.[30] We also presented neutral face stimuli to examine whether female subjects with FraX would exhibit heightened activation of regions indicative of heightened arousal to facial stimuli independent of emotional expression. To further analyze the association of genetic “dose” and cognition with engagement of networks associated with affect regulation and perception, we examined whether brain activation correlated with FSIQ and FMRP level.

METHOD

Subjects

Ten female subjects with FraX and ten TD control subjects were recruited. We recruited only female subjects to remove intersubject variance attributable to sex and to maintain generally comparable IQs between groups.

All subjects were right-handed.[31] The FraX group had a mean ± SD age of 16.4 ± 4.9 years (range 9.7–24.0 years). The TD controls were matched for age (15.6 ± 4.2, range 8.4–22.9 years), with no significant differences found between groups (t_{18} = 0.3, p = .70). The *FMR1* full mutation was confirmed for all female subjects with FraX using standard DNA (Southern blot) analysis. The FraX FMRP levels were ascertained using immunostaining techniques to calculate the percentage of peripheral lymphocytes containing FMRP.[32] Written informed assent and/or consent were obtained from all of the subjects and/or parents. The human subjects review committee at Stanford University School of Medicine, Stanford, California, approved all protocols.

IQ was measured using the WISC III[33] for subjects younger than 17 years and the WAIS III[34] for subjects ages 17 years and older. The IQs of two TD subjects were assessed using the Wechsler Abbreviated Scale of Intelligence.[35] The FSIQ scores showed a strong trend toward a significant difference between groups (FraX = 91 ± 16.2, range 75–124; TD = 106.1 ± 15.7, range 79–128) (t_{18} = 2.1, p = .052).

MRI Preparation

Before the scan, subjects were given behavioral preparation using a standardized MRI preparation protocol (http://spnl.stanford.edu/participating/mri_prep/intro.htm). Furthermore, research personnel worked with each FraX subject to ensure that she was capable of understanding and performing the task.

Experimental Stimuli

Color photographs of faces from 120 college-age models were taken against a common uniform background at a distance of approximately 2 m. Thirty photographs (15 half male) from each of four categories were used: happy, sad, neutral, and scrambled faces. Emotional and neutral faces were scrambled to create scrambled face stimuli, thereby maintaining consistent spatial frequency across conditions.

Experimental Paradigm

The event-related task used a jittered stimulus presentation, with a mean interstimulus interval of 1,572 milliseconds (SD 1,805 milliseconds) and a range of 0.25 to 4.25 seconds. Stimuli were presented using PsyScope software, (http://psyscope.psy.cmu.edu), which also triggered the initiation of the functional MRI (fMRI) scan by sending a transistor–transistor logic pulse to the scanning processor. Stimuli were projected onto a screen attached to the head coil. The subjects looked directly upward at a mirror to view the stimuli. Each stimulus was presented for 1,750 milliseconds, followed by a 500-millisecond duration fixation cross. Subjects were instructed to use their right index, middle, and ring fingers to press, using a button box, a left button if the person in the photograph appeared happy, a middle button if the person appeared sad, and a right button if a neutral or scrambled face appeared. Responses and reaction times (RTs) were recorded within a time window of 150 and 2,000 milliseconds after the stimulus. Each subject performed two 60-trial (15 of each stimulus category) runs of the event-related task, with each run lasting 4 minutes 14.20 seconds (Fig. 1A).

MRI Scanning and Imaging Data Analysis

Images were acquired on a 3-T scanner (Signa, General Electric) using a standard GE whole-head coil. The scanner runs on an LX platform, with gradients in “MiniCRM” configuration (35 mT/m, slew rate 190 $mT \cdot m^{-1} \cdot second^{-1}$), and has a 3-T 80-cm magnet (Magnex Scientific, Varian Inc.). A custom-built head holder was used to minimize head movement. To maximize magnetic-field homogeneity, an automatic shim was applied. Twenty-eight axial slices (4-mm thick, 0.5-mm skip) parallel to the anterior-posterior commissure covering the whole brain were imaged with a temporal resolution of 2 seconds using a T_2*-weighted gradient echo spiral pulse sequence (repetition time = 2,000 milliseconds, echo time = 30 milliseconds, flip angle = 80°, and 1 interleave).[36] The field of view was 200 × 200 mm^2, and the matrix size was 64 × 64, which gave an in-plane spatial resolution of 3.125 mm.

Inverse Fourier transform was used to reconstruct images for each of the time points into 64 × 64 × 18 image matrices (voxel size, 3.75 × 3.75 × 4.5 mm^3). Statistical parametric mapping (SPM2, www.fil.ion.ucl.ac.uk) was used to preprocess all fMRI data, including

realignment, normalization to stereotaxic Montreal Neurological Institute coordinates, and 4-mm smoothing. For each subject, a *t*-score image was generated for each contrast of interest. Individual contrast images were combined into a group image using a random-effects model, which provides for stronger generalization to the population.[37] Significant clusters of activation for each contrast and correlation were determined using the joint expected probability distribution,[36] with height ($p < .05$) and extent ($p < .05$) thresholds corrected at the whole-brain level. Differences in FSIQ and performance accuracy were observed between groups and were therefore regressed out in a secondary analysis. Montreal Neurological Institute coordinates were converted to Talairach coordinates (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Activation foci were superimposed onto high-resolution T_1-weighted images and localized with reference to the stereotaxic atlas of Talairach and Tournoux.[38] Because the contrasts examined in this study were chosen a priori, activations from other contrasts are not reported.

Within the FraX group, we examined the relation between FMRP and brain activation to each contrast of interest. Using the between-groups contrast in which the TD group showed greater activation than the FraX group, we examined the relation between FSIQ and brain activation to each contrast of interest. Random-effects analysis was performed with FMRP or IQ as a covariate to determine brain regions that show FMRP- and IQ-related activation.

RESULTS

Behavioral Data

Collapsing the percent accuracy data across both runs and all conditions, both FraX (65.8% ± 13.9%) and TD groups (81.8% ± 19.9%) performed the task above chance (Fig. 1B). Independent-samples *t* tests (two-tailed) were conducted, revealing a statistical difference in accuracy between groups ($t_{18} = 2.2$, $p = .043$). Examining the data during both runs for each expression, the FraX group was significantly less accurate at recognizing neutral faces (40.0% ± 30.1%) when compared with the TD group (71.0% ± 35.1%; $t_{18} = 2.1$, $p = .048$, Cohen $d = 0.948$). However, the FraX group was not statistically different from the TD group in the correct identification of happy faces (FraX: 83.0% ± 17.1%; TD: 81.7% ± 20.7%; $t_{18} = 0.2$, $p = .877$, Cohen $d = 0.068$). Performance for sad faces was lower for the FraX group (55.3% ± 30.4%) when compared with the TD group (78.3% ± 22.4%), although this difference did not reach statistical significance ($t_{18} = 1.9$, $p = .070$, Cohen $d = 0.861$), perhaps because of low power. Performance for scrambled faces was significantly lower for the FraX group (82.3% ± 15.8%) when compared with the TD group (96.3% ± 5.5%; $t_{18} = 2.6$, $p = .016$, Cohen $d = 1.183$; Fig. 1C).

No differences in RT for correct responses were found between groups for neutral, happy, sad, and scrambled faces ($p > .05$). However, the TD group showed significant differences in RT for correct responses for happy faces compared with sad faces ($t_9 = -4.29$, $p = .002$, Cohen $d = -0.750$) and for happy faces compared with neutral faces ($t_9 = -2.81$, $p = .020$, Cohen $d = -0.572$), such that happy faces (750.03 ± 187.03 milliseconds) were identified more rapidly than were sad faces (895.28 ± 200.23 milliseconds) and neutral faces (886.66 ± 281.50 milliseconds). No other differences in RT for correct responses between conditions were observed within group, neither for the FraX group nor for the TD group (Fig. 1C). No

correlations between FSIQ, RT, and accuracy were found for either the TD group or the FraX group. Furthermore, the FraX group showed no correlation between FMRP levels and these behavioral indices ($p > .05$).

fMRI Data

Within-Group Analysis—Results of within-group analyses can be found in Supplemental Digital Content Tables A to C, at http://links.lww.com/A570, http://links.lww.com/A571, and http://links.lww.com/A572, respectively.

Between-Group Analysis

Sad faces minus neutral faces: When IQ and performance accuracy for sad faces were regressed out of the analysis (designated as nuisance variables), the FraX group did not show any regions with significantly greater activation compared with the TD group. However, three clusters of activation remained significant for the TD>FraX comparison. One circumscribed cluster peaked in the right cuneus. Another cluster peaked in the right precentral gyrus, with activation extending to the right postcentral gyrus and the insula. A final cluster peaked in the left inferior parietal lobe, with activation extending to the left insula and the left precentral gyrus (Table 1, Fig. 2A).

Happy faces minus neutral faces: The TD group did not show any regions with significantly greater activation for happy faces compared with the FraX group when IQ and performance accuracy were regressed out of the analysis. However, three clusters of activation remained significant for the FraX>TD comparison. One cluster peaked in the left lingual gyrus, with activation extending to the right precuneus and the left cuneus. Another cluster peaked in the right precentral gyrus, with activation extending to the right middle frontal gyrus and the right insula. The final cluster was observed peaking in the left precentral gyrus, with activation extending to the left postcentral gyrus (Table 2, Fig. 2B).

Neutral faces minus scrambled faces: The FraX group did not show any regions with significantly greater activation compared with the TD group when IQ and performance accuracy for neutral faces were regressed out of the analysis. However, three clusters of activation remained significant for the TD>FraX comparison. One cluster peaked in the right cingulate gyrus and extended to the right ACC. A more circumscribed cluster peaked in the precuneus. The final cluster was observed peaking bilaterally in the dorsal ACC (dACC; Table 3, Figs. 3A, B).

Sad faces minus scrambled faces: With IQ and performance accuracy regressed out of the analysis, the female subjects with FraX did not show any regions with greater activation than the TD group for sad faces. However, four clusters of activation remained significantly different for the TD>FraX comparison. One cluster was observed peaking bilaterally in the lentiform nucleus and extended to the left claustrum, putamen, and caudate (Figs. 3C, D). Another cluster observed peaked in the left superior frontal gyrus and extended to the left middle frontal gyrus. A third cluster was observed peaking in the left inferior parietal lobule. The final cluster was seen peaking bilaterally in the precuneus (Table 1).

Happy faces minus scrambled faces: When IQ and task performance were regressed out of the analysis, no activation remained significantly different between groups, neither for the TD>FraX comparison nor for the FraX>TD comparison (Table 2).

Correlational Analyses

Fragile X mental retardation protein: To examine whether variation in FMRP was related to observed brain activation, a post hoc covariate analysis between FMRP and blood oxygen level–dependent (BOLD) signal intensity was performed for the FraX group. In all three contrasts, FMRP levels correlated positively with activation in the dACC (Supplemental Digital Content Table D, at http://links.lww.com/A573; Fig. 4). When IQ was covaried out of the analysis, a significant positive correlation was observed, with activation in the dACC for the happy minus scrambled contrast only. Other regions where BOLD activation significantly correlated with FMRP are reported in Supplemental Digital Content Tables D and E, at http://links.lww.com/A573 and http://links.lww.com/A574 and Figure 4.

IQ: To examine the association of IQ with neural activation in our research subjects, a post hoc covariate analysis between FSIQ and BOLD signal intensity was performed for both the TD and the FraX groups. For the TD>FraX comparison, a significantly greater positive correlation with IQ and activity in the right dACC was observed for neutral minus scrambled faces (Supplemental Digital Content Table F, at http://links.lww.com/A575). For the FraX>TD comparison, a significantly greater negative correlation with IQ and insula activation was observed for neutral minus scrambled faces (Supplemental Digital Content Table G, at http://links.lww.com/A576). Other regions where BOLD activation significantly correlated with IQ are reported in Supplemental Digital Content Tables F and G.

DISCUSSION

To our knowledge, these results are the first to identify the neural underpinnings of emotion attribution in FraX. Consistent with the behavioral literature, when compared with the TD group, the female subjects with FraX were generally comparable in their ability to correctly identify happy faces.[11] Inconsistent with the behavioral literature,[11] when compared with the TD group, the female subjects with FraX showed a trend toward a significant reduction in the correct identification of sad faces. The TD group took significantly longer to identify the sad faces within our stimulus set when compared with the happy faces. This suggests that the sad faces stimuli were not as readily identifiable as were the happy faces. We therefore interpret the findings to reflect that the female subjects with FraX may be poorer at recognizing emotional faces that are more ambiguous in expression. Consistent with this interpretation, the TD group took significantly longer to classify the neutral faces within our stimulus set when compared with the happy faces. Correspondingly, the FraX group was significantly more impaired in the identification of neutral faces when compared with the TD group. Although the paucity of research on neutral face identification precludes comparison with a full-mutation sex-matched group, these findings bear resemblance to one study of FraX premutation male subjects that found significantly poorer neutral face categorization relative to sex- and age-matched controls.[39] In the present study, no significant correlations between IQ and behavioral performance were found for the TD

group, and no significant correlations were found between behavioral performance, IQ, and FMRP level for the FraX group. These results are not surprising, given the sample size and the putative effects of environmental factors on cognitive outcome in this condition.[3,4,39,40]

Once differences in task performance and IQ were regressed out of the initial analysis, our fMRI results showed prominent between-group differences in brain regions involved in social affective processing and anxiety when processing both emotional and neutral faces. Although the happy minus scrambled faces contrast revealed no differences in activation between groups, the FraX group showed increased activation in many regions, including the right insula, for the happy minus neutral faces contrast. The TD group showed significantly greater activation than the FraX group in the left caudate for sad faces relative to scrambled faces. Although activation differences in the left caudate were not present between groups for sad faces relative to neutral faces, the TD group showed greater activation than the FraX group in the left insula for sad faces relative to neutral faces. The TD group also showed significantly greater activation than the FraX group in the dACC for neutral faces relative to scrambled faces. Interestingly, the FraX group showed a significant positive correlation between BOLD activation and FMRP level for each of the three contrasts in the dACC. After controlling for differences in IQ, a positive correlation between BOLD activation and FMRP level remained for the contrast between happy and scrambled faces. The activation differences observed in the caudate and dACC are in line with our a priori hypotheses and may be a specific neurophenotypic characteristic of FraX. Therefore, the following discussion emphasizes these regions.

For neutral faces relative to scrambled faces, significantly greater activation was found bilaterally in the dACC for the TD group compared with the FraX group when controlling for IQ and task performance. Interestingly, a significantly greater positive correlation between IQ and right dACC activity was observed for neutral faces compared with scrambled faces for the TD group relative to the FraX group. Developmental studies have shown that neutral faces can be perceived as ambiguous, presumably not representing a signal of neutrality (see, for example, Reference 41). The dACC may be involved in contextually driven modulation of mental or physical bodily arousal states in both human and nonhuman primates.[42–44] Human and comparative studies suggest that the ACC is involved in self-induced reductions in anxiety[45] and the regulation of the hypothalamic–pituitary–adrenal (HPA) axis—a major part of the neuroendocrine system that controls stress response.[6,46,47] One study found a correlation between changes in baseline blood flow in the ACC and salivary cortisol while subjects performed a mental arithmetic task,[48] suggesting that disruption of the ACC may impede top-down control of the HPA axis in typical populations. The HPA axis has been shown to be dysfunctional in FraX.[6,49] *FMR1* KO mice show disruption of long-term potentiation in the ACC[20] and dysfunctional HPA function.[50] Significant positive correlations between FMRP and BOLD signal in the dACC were observed for all conditions; however, the positive correlation between FMRP and activity in the dACC remained only for the happy faces minus scrambled faces contrast after controlling for differences in IQ. These findings speak to the complex interplay between cognition and FMRP level and suggest that higher cognitive ability and FMRP level may be linked with developing and maintaining successful coping strategies or cognitive appraisals[51] in putatively socially anxiogenic situations. Other work from our group shows

activation in the right ACC to be disrupted in female subjects with FraX,[9] thus further supporting the premise that aberrant activation of the ACC may contribute to social anxiety in FraX. Our dACC findings suggest that, in comparison to the TD group, the FraX group may be less able to use top-down mechanisms to modulate emotional responses toward faces, independent of emotional expression.

Findings from our emotion contrasts support the premise that facial stimuli, and not facial expressions per se, may elicit heightened emotional responses for the FraX group compared with the TD group. A significant reduction in caudate activation was observed in the FraX group relative to the TD group for sad faces compared independently with scrambled faces but not for sad faces compared independently with neutral faces, once task performance and IQ were regressed out of the primary analyses. This finding suggests that BOLD activation differences were mainly attributable to faces and not to sad facial expressions. One explanation for this finding is that facial stimuli independent of emotional expression elicited the reductions in caudate activation observed in the FraX group. Dramatically increased caudate nucleus volumes have been observed in both male and female subjects with FraX and are associated with decreases in IQ—a trend opposite to the pattern observed in TD subjects.[40] Reduced FMRP levels in FraX may inhibit group 1 metabotropic glutamate receptor–dependent protein synthesis and impair dendritic spine elimination, leading to volumetric increases in brain areas[52] such as the caudate. The caudate is an integral component of the cortico-striato-thalamo-cortical loop. This network has been implicated in the regulation of mood and social behavior.[53,54] As part of the cortico-striato-thalamo-cortical loop, the caudate has been suggested to facilitate the regulation of prepotent emotional responses,[55] with recent fMRI studies showing abnormal caudate function in social phobics.[56] Other groups have suggested that striatal dysfunction may impair the natural fluidity of social motor functions, such as eye and mouth movements, which may lead to an inability to respond to new social situations.[57] In addition, it has been proposed that striatal dysfunction may lead to biasing social events as negative.[58] Our group has suggested that disruption to the caudate may disrupt anxiety and socioemotional behavior in FraX.[4] Evidence from lesion studies have implicated the caudate in dyscontrol of emotion,[59] depression, inattention, high distractibility, and frequent expressions of fear[60]—all symptoms commonly occurring in people with FraX. Taken together, the FraX group may be less able to inhibit emotional responses, particularly toward faces.

Whereas caudate activation was not found to correlate with either FMRP or IQ, a significantly greater negative correlation between IQ and right insula activity was observed for neutral faces compared with scrambled faces for the FraX group compared with the TD group, suggesting that lower levels of IQ may be associated with increased affective response. One review suggests that the anterior insula plays a role in anxiety and is perhaps involved in exaggerating predictive cues of prospective bodily states of aversive arousal.[61] Anatomic projections to the hypothalamus are important in the regulation of cardiovascular and endocrinologic response to stressful situations (see, for example, Reference 62), whereas the afferent projections of the insula to the ACC enable modulation of attentional resources.[61,63] Defective insula functioning is a commonly described feature of many emotional disorders, including simple phobia, and panic disorder.[64–67] In both TD subjects and subjects with generalized social phobia, anticipation of emotionally aversive events has

been shown to activate the insula.[66,68] The insula has also been activated during exposure to aversive stimuli[68] and autonomic arousal.[69] Collectively, these data correspond with the elevated state of arousal observed in people with FraX, which includes a physiological phenotype of elevated baseline, tonic and phasic electrodermal activity/response,[49,70,71] elevated heart activity,[72] elevated cortisol levels,[6] and lower levels of vagal tone.[72] The significantly greater negative correlation observed between right insula activation and IQ in the FraX group as compared with the TD group may indicate that subjects with FraX with lower cognitive ability may be more aroused by facial stimuli than subjects with FraX with higher cognitive ability.

An emotion-specific effect was also observed in the insula whereby the FraX group elicited significantly greater activation than the TD group in the right insula for happy faces relative to neutral faces, whereas the TD group elicited significantly greater activation than the FraX group in the left insula for sad faces relative to neutral faces. Although these data are in need of replication before any firm conclusions can be drawn, findings could indicate that the FraX group is more aroused by happy faces when compared with the TD group. Happy faces possess an inherent positive reinforcement value, which could lead to increased arousal in the FraX group. By contrast, the greater activation in the left insula for the TD group relative to the FraX group for sad faces could indicate that the TD group is more aroused by sad faces than the FraX group, perhaps resulting from increased empathic responding by the TD group.

The amygdala and prefrontal cortex are two brain regions often suggested to modulate emotion. The functional relation between the amygdala and the prefrontal cortex has been suggested to play an important role in anxiety and affective processing style.[73] The amygdala is suggested to respond selectively to socially relevant stimuli, especially negative emotive stimuli.[17,74–81] In nonhuman primates, lesions to the amygdala lead to an interference in fear response conditioning[62] and an inability to assign negative value to stimuli.[82] In relation to the female subjects with FraX, a diffusion tensor imaging study from our group showed reduced frontostriatal fractional anisotropy,[2] thus suggesting that cortical-subcortical connections are disrupted in FraX. Our within- and between-group analyses of the TD group showed significantly greater activation of the right amygdala for sad faces compared with scrambled faces than the FraX group. However, this difference did not remain significant once IQ and performance were regressed out of the analysis, suggesting that the amygdala may be more susceptible to disruption under conditions of general cognitive impairment. These results highlight the importance of interrogating results to delineate functional activation differences resulting from group differences in performance or IQ from activation differences that represent pathognomonic characteristics of a disorder.

Three main limitations of our study should be considered. One limitation is that separate response buttons were not used for neutral and scrambled faces. We chose not to use separate buttons for these two conditions because our behavioral pilot testing revealed that the use of four response buttons was more confusing to all participants. We therefore chose to simplify the task to the use of three buttons across both groups of subjects so as not to confound the data with between-group task differences. Given that the neutral and scrambled faces were considered as baseline conditions for the behavioral task, we chose to consolidate

these button presses. Another limitation is that dysfunction in the ACC, the amygdala, and the caudate are not specific to anxiety disorders and may represent other cognitive processes (e.g., error processing, working memory). A final limitation is that the interstimulus interval we used was relatively short and may contribute to decreased power after covariate analyses to detect potential alterations in region of interests previously implicated in FraX syndrome and related disorders.

In conclusion, we provide support that female subjects with FraX perform behaviorally similar to sex- and age-matched TD controls when asked to identify happy facial emotions. However, emotionally ambiguous (neutral) and emotionally laden (i.e., sad, happy) faces may elicit heightened levels of emotion associated with social anxiety, irrespective of differences in correct emotion attribution. Our fMRI results support this conclusion, although additional imaging studies of emotion attribution in FraX are warranted. We further suggest that FMRP levels and IQ may directly or indirectly influence the emotion circuit in FraX, particularly in paralimbic structures like the ACC. Such disruption may lead to a reduced ability to regulate anxiety levels in social encounters and help to account for the elevated social anxiety and avoidance behaviors typically observed in FraX. More broadly, we have demonstrated that FraX syndrome, a single-gene disorder, may result in a cascade of neural effects that disrupt social behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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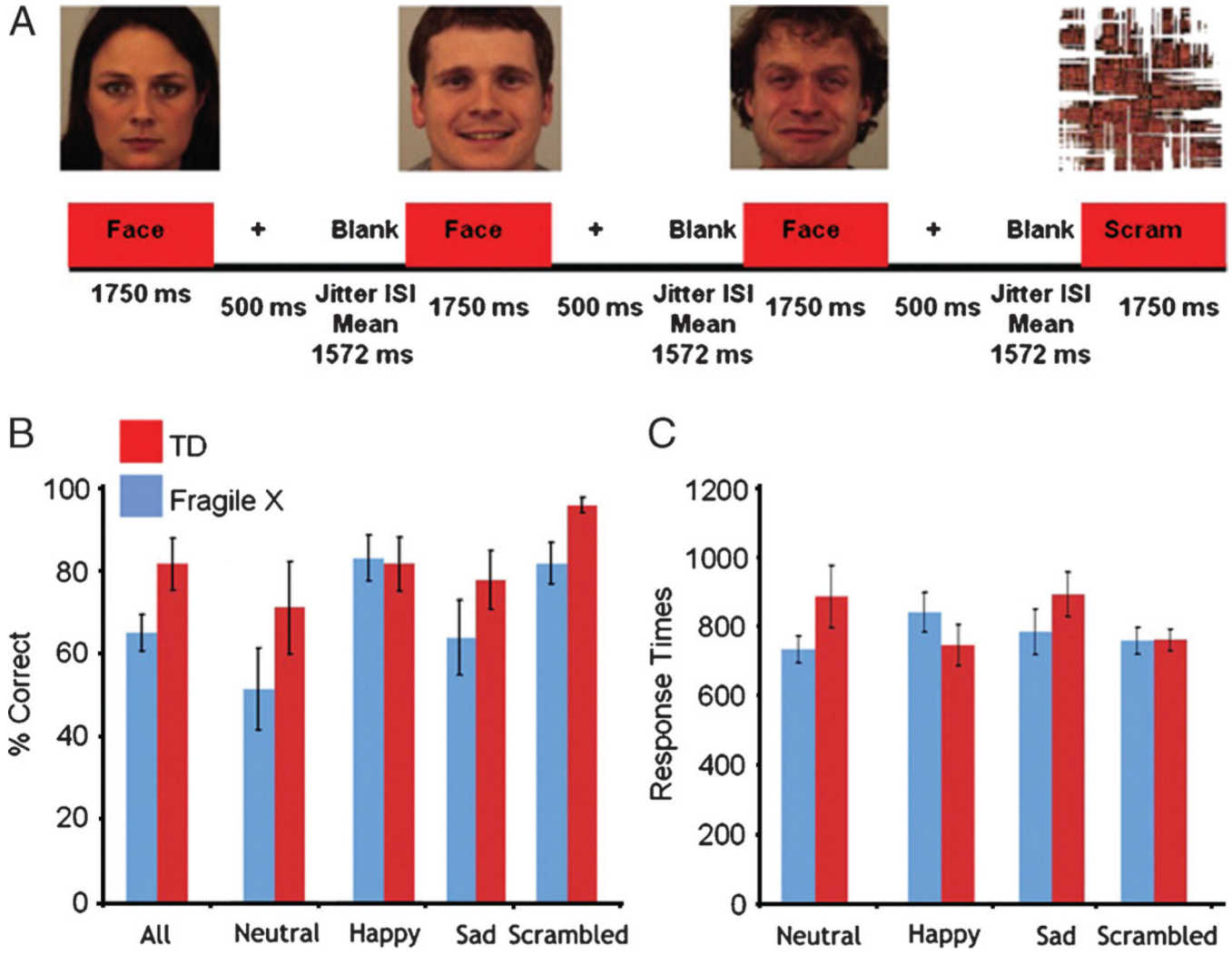

Fig. 1.

Paradigm illustration (A), behavioral results in average percent correct for each stimulus category and each group (B), and behavioral results in average response time for each stimulus category and each group (C). Error bars represent standard error of the mean.

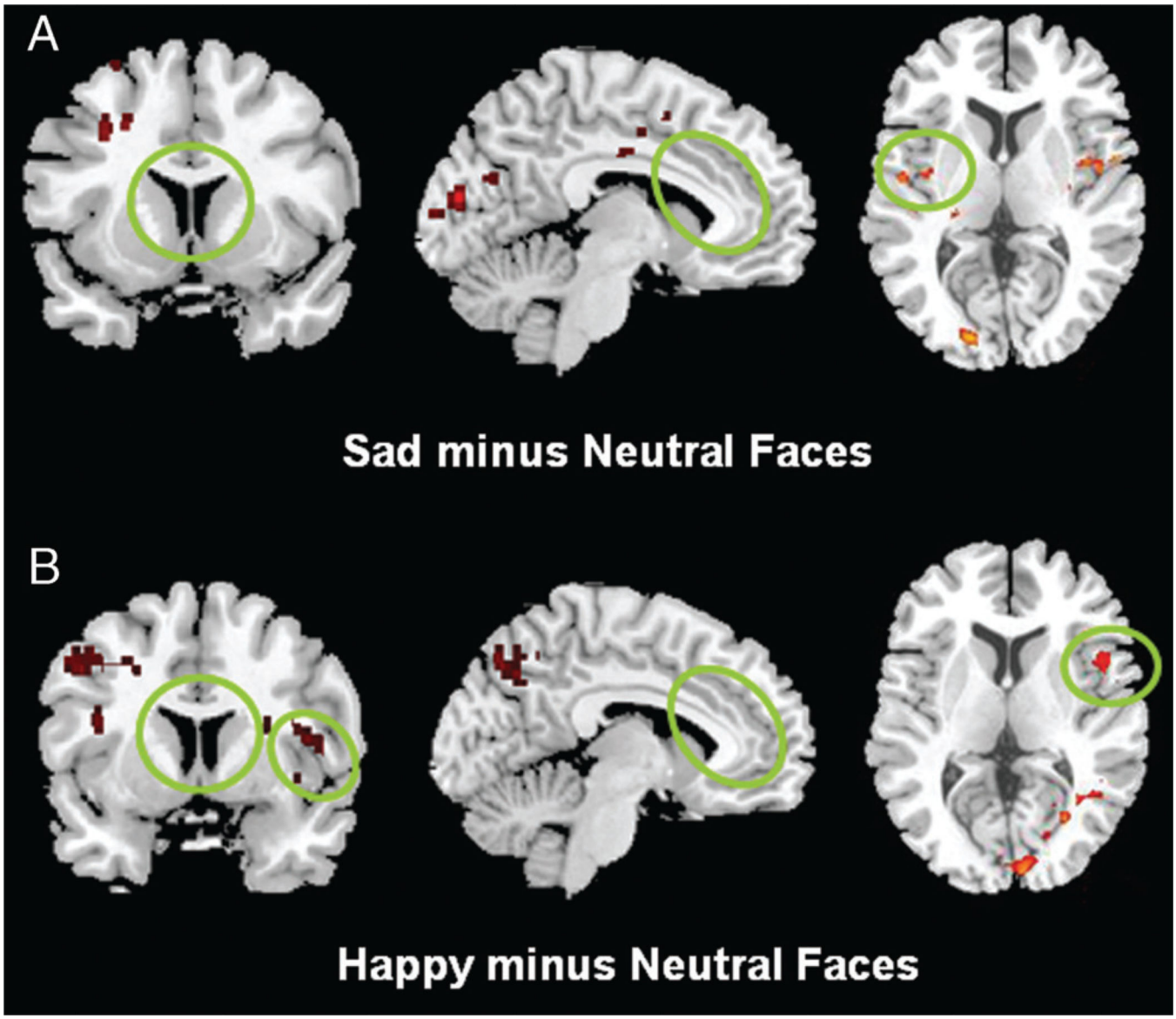

Fig. 2.

Between-group comparisons against neutral baseline. A, Regions where the typically developing (TD) group showed greater activation than the fragile X (FraX) group for sad face minus neutral face contrast. B, Regions where the FraX group showed greater activation than the TD group for happy face minus neutral face contrast. Brain regions of interest are circled in green.

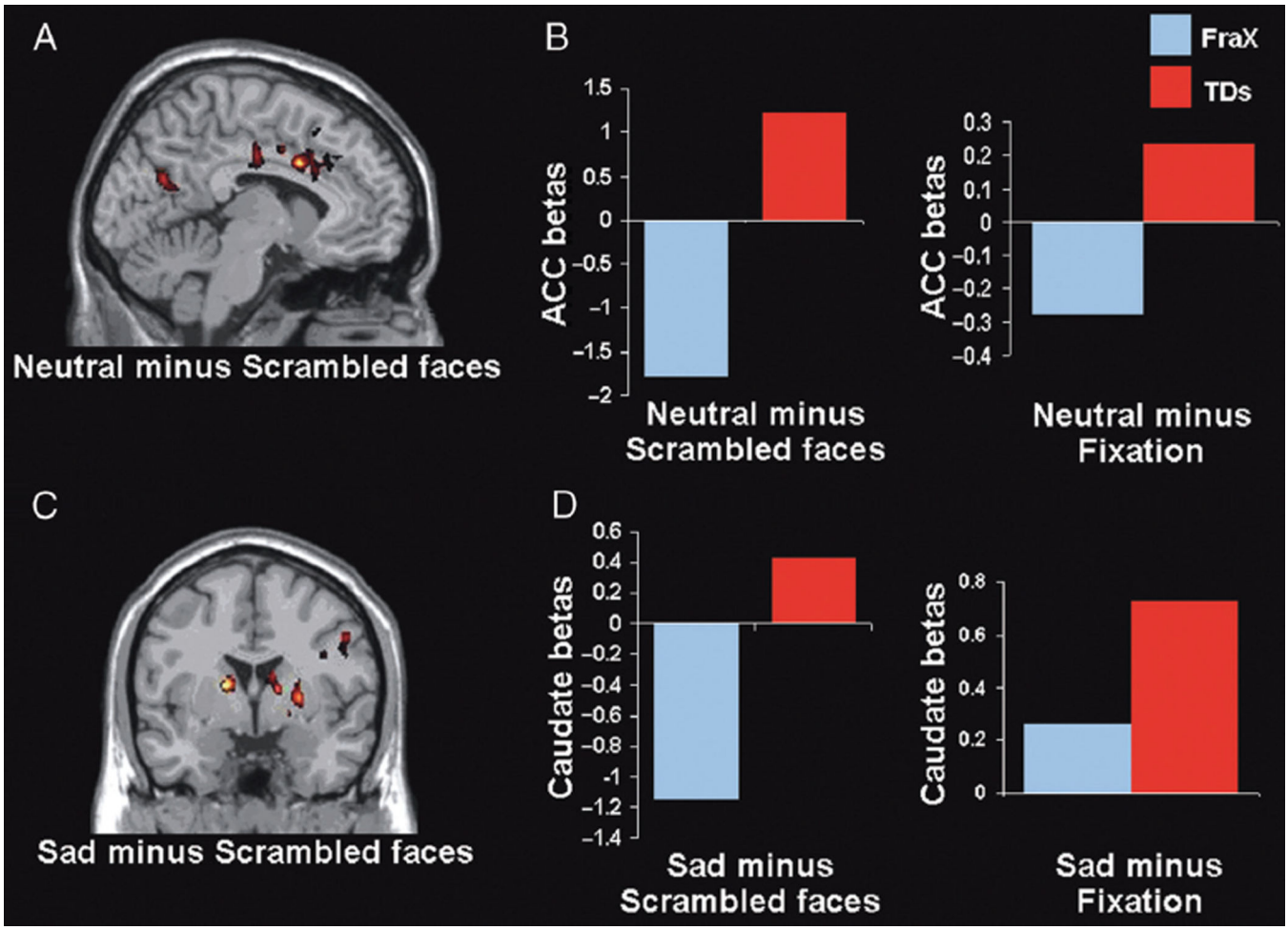

Fig. 3.

Between-group a priori regions of interest with greater activation. A, Greater activation was observed in the dorsal anterior cingulate cortex of the TD controls relative to the FraX group for neutral face minus scrambled face contrast (IQ and task performance covaried out). B, Differences observed between groups in peak coordinate (Talairach coordinates: 6, 11, 29) for neutral face minus scrambled face baseline and for neutral face minus fixation baseline. C, Greater activation was observed in the caudate of the TD controls relative to the FraX group for sad faces minus scrambled faces (IQ and task performance covaried out). D, Differences observed between groups in peak coordinate (Talairach coordinates: −26, 2, 4) for sad face minus scrambled face baseline and for sad face minus fixation baseline.

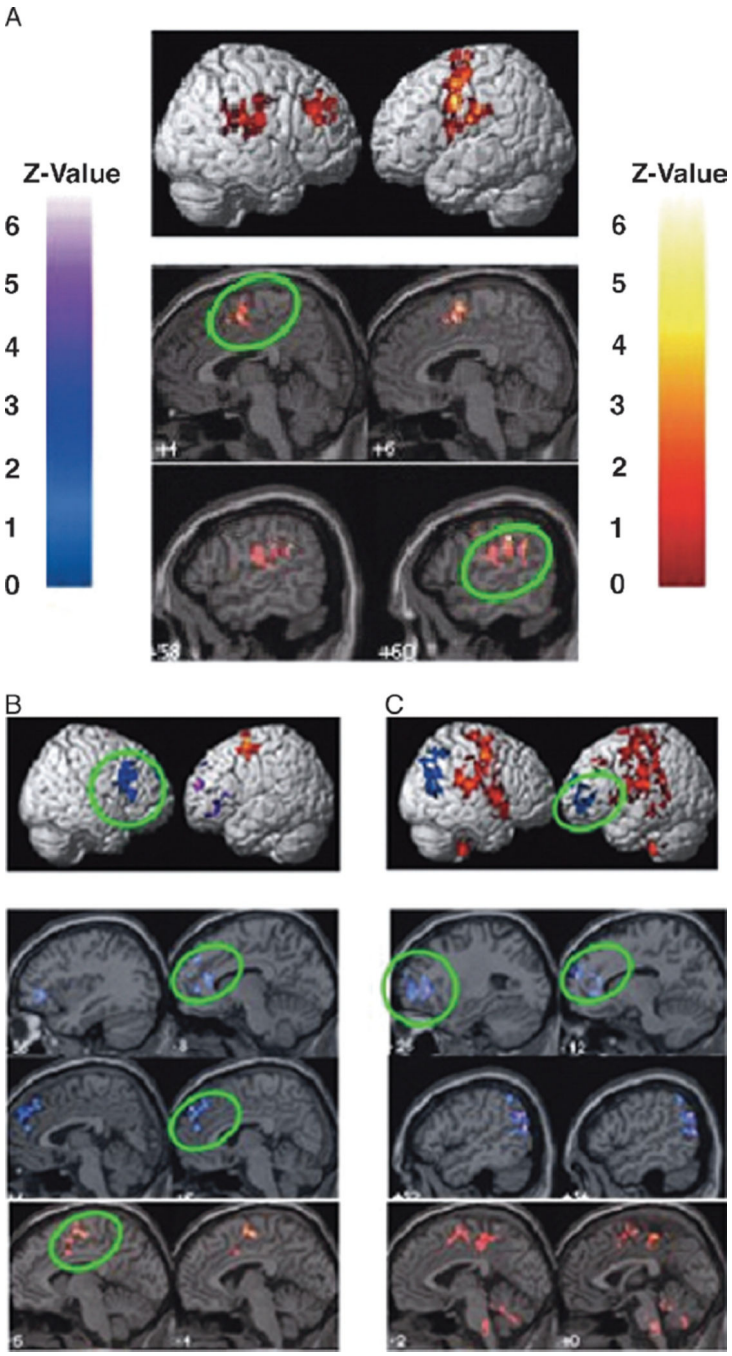

Fig. 4.

Correlations between fragile X mental retardation protein and facial emotion. Positive correlations with blood oxygen level–dependent signal in subjects with FraX are shown in orange, and negative correlations with blood oxygen level–dependent signal are shown in blue for all contrasts. A, Neutral faces minus scrambled faces. B, Happy faces minus scrambled faces. C, Sad faces minus scrambled faces. Numbers represent corresponding Talairach coordinates.

TABLE 1

Coordinates in Talairach Space and Associated Peak *z* Scores Showing the BOLD Differences for Interactions of Sad Faces Minus Scrambled Faces and Sad Faces Minus Neutral Faces

					Coordinates		
Brain Regions	**BA**	***p***	**Cluster Size**	***z* Scores**	**x**	**y**	**z**
Typically developing group versus fragile X group (accuracy, IQ covaried out), sad minus scrambled							
L lentiform nucleus, L putamen, L claustrum, L caudate, R lentiform nucleus, R putamen	—	<.001	1,420	3.79	−26	2	4
L superior frontal gyrus, L middle frontal gyrus	9/10	<.001	985	3.72	−18	45	36
L inferior parietal lobule	40	<.044	507	3.42	−30	−42	52
R precuneus, L precuneus	31/7	<.001	891	3.33	26	−72	29
Typically developing group versus fragile X group (accuracy, IQ covaried out), sad minus neutral							
R cuneus	18/17	<.030	522	3.897	8	−83	19
R precentral gyrus, R postcentral gyrus, R insula	4/13	<.001	2,197	3.834	24	−20	58
L inferior parietal lobule, L insula, L precentral gyrus	40/13/6	<.013	591	3.399	−57	−20	23

Note: BA = Brodmann area; BOLD = Blood oxygen level–dependent; L = left; R = right.

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TABLE 2

Coordinates in Talairach Space and Associated Peak *z* Scores Showing the BOLD Differences for Interactions of Happy Faces Minus Scrambled Faces and Happy Faces Minus Neutral Faces

					Coordinates		
Brain Regions	**BA**	***p***	**Cluster Size**	***z* Scores**	**x**	**y**	**z**
Fragile X group versus typically developing group (accuracy, IQ covaried out), happy minus scrambled							
None							
Fragile X group versus typically developing group (accuracy, IQ covaried out), happy minus neutral							
L lingual gyrus, R precuneus, L cuneus	19/31/17	<.001	2,212	4.78	−30	−62	7
R precentral gyrus, R middle frontal gyrus, R insula	6/9	<.026	558	3.88	40	0	35
L precentral gyrus, L postcentral gyrus	43/4/44	<.001	1,025	3.52	−61	−5	13

Note: BA = Brodmann area; BOLD = Blood oxygen level–dependent; L = left; R = right.

TABLE 3

Coordinates in Talairach Space and Associated Peak *z* Scores Showing the BOLD Differences for Interactions of Neutral Faces Minus Scrambled Faces

					Coordinates		
Brain Regions	**BA**	***p***	**Cluster Size**	***z* Scores**	**x**	**y**	**z**
Typically developing group versus fragile X group (accuracy, IQ covaried out), neutral minus scrambled							
R cingulate gyrus, R anterior cingulate cortex	24/32	<.001	1,389	4.37	6	11	29
R precuneus	31/7	<.002	830	3.88	12	−61	29
R dorsal anterior cingulate	24/31	<.024	575	3.48	14	−4	41

Note: BA = Brodmann area; BOLD = Blood oxygen level–dependent; L = left; R = right.