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Title: **Aberrant neurocognitive processing of fear in young girls with Turner syndrome**

Running Title: Fear processing in Turner syndrome

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Abstract

Appraisal of fearful stimuli is an integral aspect of social cognition. Neural circuitry underlying this phenomenon has been well-described, and encompasses a distributed network of affective and cognitive nodes. Interestingly, this ability to process fearful faces is impaired in Turner syndrome (TS), a genetic disorder of females in which all or part of an X chromosome is missing. However, neurofunctional correlates for this impairment have not been well-studied, particularly in young girls. Given that the core features of TS include X chromosome gene haploinsufficiency and secondary sex hormone deficiencies, investigation of fearful face processing may provide insights into the influence of X chromosome gene expression on this network. Therefore, we examined behavioral and neural responses during an explicit emotional face labeling task in 14 prepubertal girls with TS and 16 typically developing age-matched controls (6-13 years). We demonstrate that girls with TS have a specific impairment in the identification of fearful faces, and show decreased activation in several cognitive control regions, including the anterior dorsal anterior cingulate cortex, dorsolateral prefrontal cortex and posterior cingulate gyrus. Our results indicate that aberrant functional activation in dorsal cognitive regions play an integral role in appraisal of, and regulation of response to fear in TS.

Keywords: Turner syndrome, fear processing, emotion, anterior cingulate

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Introduction:

The ability to process emotional facial stimuli is a highly developed and integral feature of social cognition. Skills in this domain have been broadly linked to adaptive social functioning (Corden et al., 2006) and deficits are evident in a range of childhood neuropsychiatric disorders (Brotman et al., 2010;McClure et al., 2007;Pavuluri et al., 2007). Impaired recognition of emotional faces is frequently described in Turner syndrome (TS), a common sex chromosome disorder in which all or part of an X chromosome is missing. TS is often characterized by short stature, cardiac, orthopedic and endocrine abnormalities, including premature ovarian failure and sex hormone deficiencies (Hjerrild et al., 2008). A neurocognitive phenotype in TS has also been well-described and includes a marked discrepancy between relatively intact verbal skills and relatively impaired performance in executive function (Lepage et al., 2011;Waber, 1979), visuospatial (Haberecht et al., 2001;Murphy et al., 1994) and arithmetic (Kesler et al., 2003) domains. In addition, individuals with TS often demonstrate specific deficits in social cognition. As an example, previous studies report difficulties with eye gaze processing (Elgar et al., 2002) and preferential fixation for the mouth region when viewing faces (Mazzola et al., 2006). Impaired recognition of emotional facial expressions has also been extensively reported (Lawrence et al., 2003;Mazzola et al., 2006;McCauley et al., 1987;Romans et al., 1998;Skuse et al., 2005) and is particularly notable for specific deficits in fear recognition compared to relatively intact discrimination of other emotions. This constellation of symptoms implicates a programmatic pattern of social cognitive deficits that are driven by X-monosomy, making TS a compelling model to investigate the influence of the X chromosome on emotional face processing.

Recent applications of functional neuroimaging have elucidated a well-described neural circuit underlying face processing. This extended network includes visual processing regions in extrastriate occipital and superior parietal cortices (Haxby et al., 2002), affective nodes, such as the amygdala and insula, which are recruited for extraction of relevant emotional information (Haxby et al., 2002;Vuilleumier et al., 2004), and top-down cognitive control regions in the anterior cingulate (ACC) and prefrontal cortices (PFC) (Hariri et al., 2003;Lange et al., 2003;Ochsner and Gross, 2005). These nodes are thought to align with two parallel pathways specialized for rapid, automatic processing in a ventral stream (Halgren et al., 2000;Liu et al.,

1999;Morris et al., 1998) and higher-order cognitive appraisal occurring in a dorsal stream (Krolak-Salmon et al., 2004;Paulmann et al., 2010). Bottom-up ventral mechanisms are thought to rapidly analyze visual inputs from the occipital lobes, including extrastriate face-specific regions in the fusiform (Bar et al., 2006;Chen et al., 2007), which converge with subcortical inputs in the amygdala (Morris et al., 1999;Vuilleumier et al., 2003). This pathway is thought to subserve unconscious, low-resolution appraisal of salient environmental cues, such as threat (Luo et al., 2007;Ohman et al., 2007), in contrast to top-down dorsal mechanisms utilizing cognitive strategies and high-resolution sensory information to disambiguate complex stimuli and facilitate recognition, while also triggering unconscious regulation processes of arousing emotional stimuli (Gobbini and Haxby, 2007;Phillips et al., 2003;Vuilleumier et al., 2001). Furthermore, these systems are thought to interface through medial PFC structures, such as the ACC, with recent evidence increasingly demonstrating that reciprocal interaction between these streams are integral to emotional face processing (Kveraga et al., 2007;Mechelli et al., 2004;Vuilleumier et al., 2001).

Furthermore neural circuits within this emotional face processing network have been found to be valence-specific , including consistent reports that amygdala activation is associated with fearful stimuli (Morris et al., 1998;Whalen et al., 1998), and more broadly, that ACC and PFC activation is associated with negative emotional stimuli at large (Etkin et al., 2011). Ventral aspects of the fearful face recognition network have been shown to be disrupted in adult women with TS (Skuse et al., 2005) in whom arousal and appraisal to fearful stimuli were found to be functionally dissociated in an implicit emotion paradigm. However, there has been no functional imaging study to date examining emotional face processing in young children with TS. This is particularly important given evidence of significant maturational changes in neural circuits subserving emotional and cognitive behavior throughout childhood and adolescence (Blakemore et al., 2010;Casey et al., 2000), including decreased gray matter volume in the amygdala during puberty in adolescent girls (Neufang et al., 2009), and significant changes in prefrontal cortices throughout puberty from late childhood through early adulthood (Ernst et al., 2006;Nelson et al., 2005). Further elaboration of emotional face processing in TS from a developmental perspective is also needed to allow a more comprehensive understanding of its contributions to well-documented problems in social cognition and

behavior during childhood in affected individuals (Hong et al., 2011;Lepage et al., 2011). Taken together with previous evidence that females are generally more accurate in perceiving emotional prosody and facial expression (Montagne et al., 2005) and that activation in the amygdala during presentation of emotional stimuli show sexually dimorphic patterns (Derntl et al., 2010;Kempton et al., 2009;Schneider et al.;Williams et al., 2005), there is compelling support for a unique role of the X chromosome in the neurobiological basis of fear recognition.

The goals of this study were to examine neural activation patterns in a sample of prepubertal girls with TS prior to estrogen replacement compared to healthy control peers using an emotional face-labeling paradigm. We hypothesized that processing of fearful facial expressions in young girls with TS reflects functional impairment of the emotional face processing circuit. Therefore, we predicted that: 1) girls with TS would demonstrate impaired classification for fearful faces and 2) girls with TS would show altered amygdala and prefrontal activity in response to fearful facial expressions.

Material and Methods:

Subjects

A total of thirty participants were included in this study, ranging in age from 6 to 13 years. Fourteen girls with TS (ages 6.92-12.92, mean 10.10±1.70) were recruited through referrals from pediatric endocrinologists, the national Turner Syndrome Society of the US network and the Center for Interdisciplinary Brain Sciences Research (CIBSR) website (http://cibsr.stanford.edu). All participants with TS had an X-monosomy genotype (45X) as confirmed by standard karyotype analysis. Sixteen typically developing (TD) participants (ages 6.17-12.67, mean 9.47±2.12) were recruited through local parent organizations and advertisements. Three of these TD controls were female siblings of TS participants. All TD participants were in good overall medical health. None of the participants reported any previous or current neurological or psychiatric diagnoses. Further criteria for exclusion included: treatment with estrogen replacement and Tanner score >2 on breast or pubic hair parent report scales (Brooks-Gunn et al.,

1987). Informed consent and assent were obtained from all families and participants and study protocols were approved by the Stanford University School of Medicine institutional review board.

Cognitive and Psychological Assessments

All participants underwent intelligence assessments using the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV),(Wechsler, 2004). Index scores for verbal comprehension, perceptual reasoning, working memory and processing speed are reported here. Independent t-tests were used to compare scores between groups, two-tailed p-values <.05 were considered significant.

Behavioral Analyses

Behavioral data during the task were analyzed using a repeated-measures analyses of variance (ANOVA), with emotion as a within-subject factor and diagnosis as a between-subjects factor. To avoid potential attentional confounds, subjects who missed or were incorrect for greater than one-third of all trials were excluded. Data was tested for assumption of sphericity using Mauchly's test. If violated, multivariate test statistics were planned as they are not dependent on the sphericity assumption. The overall model, main effects and interaction terms were considered significant at p<.05. In the case that the interaction term was significant, follow-up pairwise comparisons between groups were conducted for each emotion at a significance level of p<.0125 (Bonferroni corrected for multiple comparisons). Additionally, there were significant differences in IQ measures between groups, with the TS cohort showing relative preservation of verbal skills and domain-specific impairments in procedural skills and working memory domains, as has been reported in TS literature. Although the use of IQ as a measure of intellectual ability in neurodevelopmental syndromes is debatable, we conducted parallel ANCOVAs using VIQ as a covariate to ensure that findings were attributable to group status and not to IQ differences.

fMRI paradigm and experimental design

The task consists of 120 color photographs of the head and shoulder region of 15 unique college-aged individuals each depicting fearful, happy and neutral expressions (Haas et al., 2009). Briefly, photographs

were taken of one hundred undergraduates trained in the facial expression of various emotional valences. Each photograph was then rated on a 5-point scale by an independent group of twenty students, with 5 being "very characteristic of the emotion" and 1 being "not at all like the emotion". Stimuli with the highest ratings for each emotional valence were used in the study and demonstrated that fearful face stimuli were rated more fearful than neutral ($t=16.01$, $p<.0001$) and happy ($t = 18.65$, $p<.001$) stimuli, neutral face stimuli were rated as more neutral than fearful ($t = 36.63$, $p <.001$) and happy ($t = 47.54$, $p=.001$) stimuli and happy face stimuli were rated as more happy than fearful ($t=61.93$, $p<.001$) and neutral ($t = 49.66$, $p <.001$) stimuli. Additionally scrambled images were created from a group of randomly selected isoluminant photographs which were split into 256 parts and reassembled in random order as described in previous studies of face processing (Haas et al., 2009;Mobbs et al., 2004).

Stimuli were programmed using ePrime software and presented to participants in the scanner via projection onto a mirror attached to the fMRI headcoil. The task was administered over two separate scan runs, each lasting 14 minutes and 42 seconds, presented at separate timepoints within a two-hour scanning session or sequentially on two consecutive days. The task was a rapid event-related design with experimental conditions of fearful, happy, neutral and scrambled stimuli. This resulted in a total of 120 photographs across the two scan sessions with 30 events for each condition. Stimuli were presented in a randomly ordered fixed sequence for all participants, each lasting for 1950ms, followed by a 50ms presentation of a blank screen with a black background. An additional 80 blank images with a black background and centered fixation cross each lasting 2000ms, were pseudo-randomly interspersed throughout the entire task, creating an effective jittered interstimulus interval (ISI) ranging from 50-6050ms, with an average ISI of 2695ms. Participants were asked to identify the emotion by pressing a corresponding key on the button box in their right hand – one button for happy expressions, one for fearful expressions and one for either neutral expressions or scrambled faces. The order of buttons correlating to emotions was fixed for all participants. Correct and incorrect responses and response times were recorded.

MRI Data Acquisition

Prior to MRI scanning, subjects participated in a mock MRI scanning session in order to familiarize themselves with the scanner environment and to implement behavioral strategies for reducing head motion. Participants were also introduced to fMRI paradigms outside of the scanner to ensure that they adequately comprehended the instructions presented in each task and were observed to correctly use the button boxes for responses. Magnetic resonance imaging was performed in the Lucas Center for Imaging at Stanford University using a 3.0T GE Signa whole body scanner (GE Healthcare Systems, Milwaukee, WI), using a standard head coil. High resolution anatomical brain images using a spoiled gradient (SPGR) echo pulse sequence were acquired for each subject (124 coronal slices, 1.5 mm thickness, repetition time (TR) = 6.40 ms, echo time (TE) = 2.10 ms, flip angle = 15°, matrix 256 x 256, field-of-view (FOV) = 220 mm) and subsequently used for localization and coregistration of functional data. A T2*-weighted gradient echo spiral-in/out pulse sequence (Glover and Law, 2001) was used to obtain functional images (TR = 2000 ms, TE = 30 ms, flip angle = 80°, matrix 64 x 64, FOV = 220 mm). Thirty oblique axial slices were acquired in parallel alignment with the ACPC (4.0 mm thickness, skip 1.0). A high-order shimming protocol was used prior to functional scans in order to correct B0 heterogeneity and avoid blurring and signal loss (Kim et al., 2002).

fMRI preprocessing

All structural images were visually inspected for motion artifact and manually aligned to AC-PC axes. Functional imaging data were preprocessed using Statistical Parametric Mapping software (SPM8, Wellcome Department for Imaging Neuroscience http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), which included correction for slice timing, realignment to the third scan in each functional series, coregistration to the individual's structural image, and reslicing to 1.5 mm cubic voxels. Motion artifacts were then corrected using in-house ArtRepair software (http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm). Images were smoothed with a 4 mm full-width-half-maximum (FWHM) Gaussian smoothing kernel, despiked using clipping and a high-pass filter, then motion-adjusted for interpolation errors from large motions. Outlier volumes demonstrating scan-to-

scan motion >0.5 mm/TR or global signal intensity fluctuations >1.5% were deweighted and repaired using interpolation between the nearest unrepaired scans. Participants were removed f further analysis if >25% of total volumes were repaired. Images were then normalized to Montreal Neurological Institute (MNI) space, using a custom DARTEL gray matter template and smoothed with a 7 mm FWHM Gaussian kernel. Post-hoc analyses for motion were conducted by examining the maximum range of motion (in mm) for each participant during each scan run and calculating total root mean square (RMS; the square root of sum of squares for all six motion parameters).

SPM analysis

Within-subject fixed-effect linear models were constructed in SPM8 using regressors for each of the face conditions and a constant for each of the two sessions. Each stimulus presentation was defined as a single event and contrasts were modeled to represent all events in each task condition (happy, fearful, neutral, and scrambled) convolved with a hemodynamic response function. Contrast images from each subject were then entered into a second-level random effects model to examine group differences in blood-oxygen-level-dependent (BOLD) signal during each emotional condition compared to the scrambled condition between TS and TD cohorts, i.e. happy-scrambled and fearful-scrambled facial expression contrasts for TS vs. TD. The scrambled face condition was selected *a priori* for baseline comparison when the experiment was designed, given previous literature that neutral faces may be interpreted as fearful in children (Cooney et al., 2006;Thomas et al., 2001). However, we also conducted parallel analyses using neutral faces as a baseline comparison (see Supplementary material). Again, though IQ may not accurately represent innate intellectual ability in neurodevelopmental syndromes, we conducted parallel second-level analyses using VIQ as a covariate. For whole-brain analyses, we corrected for multiple comparisons using AFNI's 3dClustSim (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) based on Monte Carlo simulations. Using a spatial-extent threshold of 234 voxels, the significance level was established at $p<.05$ corrected.

Results:

Demographics and Cognitive Assessments

Final analyses included 14 girls with TS and 16 TD controls. Ages were not significantly different between groups as outlined in Table 1. Scores on cognitive assessments were also compared between groups and TD controls scored significantly higher on all WISC-IV measures, including FSIQ ($p<.001$), VCI ($p=.028$), PRI ($p<.001$), WMI ($p<.001$), and PSI ($p=.002$), see Table 1.

(Table 1, Demographics and Cognitive Assessments).

Behavioral Data

Overall scores of behavioral accuracy rates were compared for each condition using repeated measures ANOVA analyses with 'emotion' as the within-subject variable and diagnostic group as the between-group variable (see Figure 1). Mauchly's test results indicated that the assumption of sphericity had been violated ($\chi^2 = 30.42$, $p < .001$), therefore multivariate tests are reported here ($\varepsilon = .662$). Both the main effect of emotion (Wilks' Lambda, $F_{3, 26} = 72.60$, $p < .001$) and the interaction between emotion and group ($F_{3, 26} = 3.79$, $p = .022$) were found to significantly impact behavioral accuracy. Follow-up pairwise comparisons for the main effect of emotion demonstrated that subjects were more accurate in identifying scrambled faces compared to fearful ($p < .001$) and neutral faces ($p < .001$) but did not meet our statistical threshold for differences with happy faces ($p = .014$). Subjects also did not show significant differences in accurate identification of happy compared to fearful ($p = .033$) or neutral faces ($p = .047$), or fearful compared to neutral faces ($p = .056$). Post-hoc pairwise comparisons of the emotion x group condition showed that girls with TS were significantly less accurate in the classification of fearful faces compared to TD controls ($p = .007$), however did not differ in accuracy for the other emotions (happy: $p = .073$, neutral: $p = .106$, scrambled: $p = .179$). Parallel analysis including VIQ as a covariate showed that the main effect of emotion continued to be significant ($F_{3, 25} = 3.16$, $p = .042$), and the interaction between emotion and group trended towards significance ($F_{3, 25} = 2.38$, $p = .094$), while the interaction between emotion and VIQ was not

significant ($F_{3, 25}$ = .505, p = .682). A repeated measures ANOVA analysis of reaction times across the four facial expression conditions was also performed and demonstrated a significant main effect of the emotion condition ($F_{3, 84}$ = 50.83, p < .001), but not for the interaction of emotion x group ($F_{3, 84}$ = .43, p = .735). Post-hoc comparisons showed that subjects responded to scrambled faces in the least time (compared to happy: p < .001, fearful: p < .001, neutral: p < .001), responded more quickly to happy compared to neutral faces (p < .001) and fearful faces (p = .003), and responded more quickly to fearful compared to neutral faces (p = .005). Parallel analysis using VIQ as a covariate showed no significant main effect of emotion ($F_{3, 81}$ = .35, p = .790), the interaction effect of emotion x group ($F_{3, 81}$ = .52, p = .670) or the interaction between emotion x VIQ ($F_{3, 84}$ = .29, p = .831). Given the low rate of accuracy in the TS group in identifying fearful expressions (55%), we conducted an additional post-hoc analysis examining mislabeling rates. For the incorrect trials during the fearful face condition, the TS group selected the 'Happy' button for 27.6% of trials, the 'Neutral/Scrambled' button for 31.5% of trials and did not press any button for 40.9% of trials.

(See Figure 2, Behavioral Performance)

fMRI Analyses

Post-hoc independent t-tests of motion parameters demonstrated no significant differences between groups during either scan run for maximum range of motion (Run 1: p=.44, TD=1.97±2.07, TS=1.43±1.68; Run 2: p=.50, TD=2.20±1.96, TS=1.67±2.26) and total RMS (Run 1: p=.53, TD=.93±1.00, TS=.74±.64; Run 2: p=.70, TD=1.00±9.56, TS=.86±1.00). Furthermore, results from second-level analyses with or without VIQ as covariate did not demonstrate differences in activation patterns, therefore only results from models with VIQ as a covariate are reported here.

Happy vs. scrambled condition

Within-group: The TD group demonstrated greater activation in the right temporoparietal junction, right amygdala/hippocampus, right superior temporal gyrus and right caudate (all p<.05, corrected) when

viewing happy face compared to scrambled face conditions. The TS group demonstrated activation in the right middle occipital gyrus, right temporoparietal junction, bilateral fusiform, right amygdala, bilateral hippocampus, posterior cingulate, and bilateral inferior/superior temporal gyri (all $p<.05$ corrected).

Between-group: At the whole-brain level, the TD group did not show any greater activation than the TS group for happy face relative to scrambled face conditions. In contrast, the TS group showed greater activation in the right inferior temporal gyrus, extending into the anterior fusiform region ($p<.05$ corrected).

Fearful vs. scrambled condition

Within-group: Whole-brain analyses demonstrated significant activations throughout the emotional face circuit for the TD group (see Table 2); TD girls exhibited greater activation for fearful face than for scrambled face conditions throughout the fusiform, amygdala, insula, parahippocampus, dorsal prefrontal cortex (PFC) and ventrolateral PFC (VLPFC) regions. In contrast, girls with TS only exhibited greater activation for fearful face than for scrambled face conditions in the fusiform, amygdala, superior temporal gyrus and VLPFC regions.

Within-group correct trials: In light of the TS group's behavioral impairment in identifying fearful faces, we conducted post-hoc analyses of neural activation during trials when fearful faces were correctly identified by modeling individual regressors for each subject using correct and incorrect trials separately. Contrasts were then modeled comparing correct (or incorrect) fearful face trials with a baseline of all scrambled trials. Results from second-level analyses demonstrated that the TS group again showed activation in the right amygdala and bilateral fusiform gyri (all $p<.05$, corrected), with an additional cluster of activation in the left amygdala that trended towards significance ($p<.1$, corrected at whole-brain level). There was no significant activation when comparing neural responses when incorrectly classifying fearful faces

compared to scrambled faces. Furthermore, there were no significant differences in activation when directly comparing correct to incorrect trials of fearful face activation in either direction.

Between-group: The TD group showed greater activation than the TS group for fearful face relative to the scrambled face condition in the right DLPFC, ACC and posterior cingulate (PCC) (all $p<.05$ corrected). In contrast, the TS group did not demonstrate greater activation than the TD group in any regions.

Between-group correct trials: Post-hoc analysis of correct trials only showed that the TD group had increased activation compared to the TS group in the right superior/middle frontal gyrus approximating DLPFC ($p<.05$ corrected), which overlaps with the cluster observed in the contrast using all fearful trials. The TS>TD contrast did not demonstrate any significant activations.

Neutral vs. scrambled condition

Within-group: The TD group demonstrated activation in the right supramarginal gyrus, bilateral middle frontal gyri, right supplementary motor area and bilateral insula (all $p<.05$, corrected). In the TS cohort, there were no significant clusters of activation when viewing neutral compared to scrambled stimuli.

Between-group: There were no group differences between TD and TS cohorts for this contrast.

Emotional faces vs. neutral baseline

Contrasts of within-group happy>neutral and fearful>neutral contrasts in the TS group, as well as between-group comparisons for these contrasts are included in Supplementary material. Results for these analyses largely complement findings using scrambled faces as a baseline (see Supplementary Figures 1 and 2).

(Insert Table 2 and Figure 3)

Discussion:

In this study, we measured BOLD responses to emotional facial expressions in young girls with TS compared to TD controls. As predicted, we demonstrated that girls with TS were less accurate in classifying fearful facial expressions compared to peers. Consistent with previous literature, we observed increased activation in an extended network of emotional face processing regions in the TD group when classifying fearful faces. In contrast, girls with TS showed reduced activation in this circuit, particularly in engagement of prefrontal cortical regions. This was confirmed by between-group comparisons where girls with TS showed relatively decreased activation in the DLPFC, ACC and PCC compared to age-matched TD controls. In comparison, we also demonstrate that both TD and TS cohorts activate relatively overlapping face processing networks when presented with happy compared to scrambled face stimuli, while between-group comparisons showed that girls with TS had relatively increased activation in the right anterior fusiform gyrus compared to TD controls.

Our data elucidate an aberrant network of emotional face processing in TS in the context of an explicit emotion-labeling paradigm. As expected for TD controls, within-sample contrasts of fearful compared to scrambled faces demonstrated activation in a broad network of regions affiliated with emotional face processing, which encompasses bottom-up affective nodes and regulatory cognitive control regions that are consistent with previous literature (Haxby et al., 2002). Individuals with TS similarly activated extrastriate visual and subcortical affective regions when presented with fearful faces, suggesting that lower-order emotion processing circuitry are appropriately recruited during exposure to fearful stimuli. However, in contrast to TD controls, there was significantly decreased activation in prefrontal regions when discriminating between fearful and scrambled facial expressions, specifically in the anterior dorsal ACC and DLPFC.

As a whole, the ACC performs a range of cognitive functions, including error detection (Rushworth et al., 2011), encoding reward values (Bush et al., 2002), and outcome-based decision making (Walton et al., 2007). However, consistent with previous classification of the ACC into a 'cognitive' posterior dorsal region and an 'affective' anterior and ventral region (Bush et al., 2000), we found significant differences in the

anterior dorsal aspect of the supragenual ACC (adACC) when comparing neural responses to fearful relative to scrambled faces between groups, which lies within the 'affective' region. Specifically, the adACC plays a prominent role in cognitive appraisal during emotional processing, particularly for negative emotional stimuli (Morris et al., 1998). This includes selective attention to (Vuilleumier et al., 2001) and rapid processing of salient emotional face information (Bush et al., 2000). Taken together with evidence that this region may also be involved in conscious appraisal of threat (Mechias et al., 2010), decreased activation in this region suggests a potential locus for impaired fear appraisal abilities in individuals with TS.

Additionally, both the adACC and lateral prefrontal regions are particularly activated for high-level emotion processing tasks that require increased cognitive effort (Vuilleumier et al., 2001). In fact, the adACC plays an important role in integrating emotion-attention interactions between parallel dorsal (cognitive) and ventral (affective) networks (Fichtenholtz et al., 2004). Here we found the adACC and DLPFC are hypoactive during an explicit emotion-labeling task in young girls with TS relative to TD controls, suggesting decreased ability to recruit higher-order cognitive control regions in a paradigm where attention must be targeted at identifying facial emotions (as opposed to viewing them passively). The framework for an emotion-attention interaction is further supported by evidence of strong connectivity between the adACC and DLPFC (Beckmann et al., 2009). In a previous study using a working memory paradigm (Bray et al., 2011), we demonstrated that the frontoparietal attention network is disrupted in TS, including regions in the DLPFC. Taken together, these results suggest that impaired top-down attentional control may also contribute to impaired face emotion labeling abilities in TS. However, as top-down attentional deficits would be expected to affect all emotional valences rather than fear alone, further explanation for valence-specific differences in our findings is warranted.

Examination of happy face stimuli in both groups demonstrated robust neural activation throughout regions that are typically recruited in response to positive stimuli. The localization of between-group differences to the right lateral fusiform region is particularly interesting given the valence-specific role that

this region plays in face processing. In fact, even beyond its inclusion in the core network for face-specific visual analysis (Haxby et al., 2000), the right fusiform plays a specialized function in face identification. Interestingly, activation in the face identity processing region is thought to occur uniquely for happy faces (Henson et al., 2002;Suzuki et al., 2011). One interpretation may be that girls with TS have increased responsiveness to happy faces compared to control peers, however this is unlikely given that the right fusiform rather than the ventral visual face network at large is activated. Additionally, it is important to note that behavioral accuracy in identifying happy faces is relatively high and comparable in both cohorts. This indicates that the emotion processing circuit for happy faces allows for correct identification of emotion in TS, therefore between-group differences in this activation pattern may be attributable to impairments in face-identity rather than emotion classification circuitry. In fact, previous literature reports that suppression of activity in this region after repeated exposure to stimuli is attenuated for happy relative to other facial emotions (Suzuki et al., 2011), although face identity is eventually thought to be mastered via semantic associations in a top-down feedback loop (Henson et al., 2002). Therefore, this finding is in keeping with our overall hypothesis that top-down inhibitory feedback is likely impaired in girls with TS compared to controls.

The dorsal stream of cognitive control regions is critical for the reciprocal modulation of the ventral affective processing stream during emotion regulation processes (Ochsner and Gross, 2005;Phillips et al., 2008). The adACC is recruited during emotion regulation processes such as reappraisal (Kalisch, 2009), implicating a putative role in the inhibition of limbic arousal (Etkin et al., 2011). This is further supported by evidence of functional connectivity between these regions and the amygdala (Stein et al., 2007), suggesting that emotional arousal is driven, in part, by bottom-up feed-forward saliency cues from the amygdala and subgenual ACC to the adACC. In turn, the adACC is thought to act as a conduit exerting negative feedback inhibition from prefrontal cortical regions on the amygdala, thereby dampening emotional arousal and facilitating fear extinction. Our finding of decreased adACC activation is particularly interesting in light of Skuse et al.'s (2005) report that adult women with TS demonstrate appropriate physiologic arousal when presented with fearful faces as measured by skin conductance responses,

however, do not show habituation of amygdala activity over the course of the task in contrast to controls. Furthermore, both the amygdala and the adACC are functionally connected to the PCC (Robinson et al., 2010;Stein et al., 2007), a region that is activated in the perception of socially relevant emotion stimuli. Interestingly, the PCC is also implicated in self-evaluation of emotional states and 'theory of mind' processes (Saxe et al., 2006). Taken together with evidence that both the adACC and PCC exert inhibitory control of amygdala activity (Stein et al., 2007), our results provide evidence for a distributed network of emotion regulation that is aberrant in TS during processing of fearful stimuli.

Hence, top-down modulatory control through higher cognitive regions appears to be impaired in TS in emotional face processing, which is not surprising given that aberrant activation in the frontoparietal network has also been identified in other cognitive paradigms such as working memory (Bray et al., 2011), visuospatial tasks (Haberecht et al., 2001) and arithmetic (Kesler et al., 2006). However, results from our behavioral data indicate that impairments in top-down control may affect emotional face processing circuitry differentially depending on emotional valence. This is consistent with extant literature indicating that developmental trajectories for emotional face processing are valence-specific even in typical development, including evidence that happy faces are recognized at an earlier age, are automatically and more rapidly processed in childhood, require fewer cognitive resources overall, and less prefrontal cortical recruitment in particular (Batty and Taylor, 2006;Durand et al., 2007;Gao and Maurer, 2010;Yurgelun-Todd and Killgore, 2006). Therefore, it is possible that negative expressions such as fearful face stimuli may require increased recruitment of dorsal prefrontal modulatory regions for higher-order emotional face processing, and as such, are more affected than other emotions in TS. This would also be largely consistent with our within-group data, which demonstrate that the TD group generally recruits a large network of regions when viewing fearful faces, while the TS group recruits a similar, but less extensive network of regions, particularly in the prefrontal cortex.

Furthermore, this framework is consistent with previous research in adult women with TS showing dissociation of emotional arousal and cognitive appraisal, with arousal being associated with right

amygdala hyperactivity and appraisal being correlated to left amygdala-fusiform connectivity (Skuse et al., 2005). Our findings that the right amygdala was particularly activated when examining correctly identified fearful face trials, and also when comparing fearful to neutral faces (see Supplementary material), provide further support for lateralized arousal effects in the right hemisphere being predominant in TS. Moreover, our data expands this model by demonstrating decreased activity in the DLPFC in the TS compared to TD group for this contrast. Given the dual role of the prefrontal cortices in dampening emotional arousal in the amygdala and cognitively processing emotional faces by acting distally on the fusiform face area, aberrant activity in prefrontal regions may provide a cohesive model for the observed deficits in children and adults with TS. Alternatively, it is possible that an independent pathway of aberrant function exists in the posterior fear-processing circuit in TS which would partly explain the emotional face processing deficits in TS and are supported by findings of decreased fractional anisotropy in white matter tracts between the fusiform and amygdala (Yamagata et al., 2011). However, effective connectivity analyses, such as graph analysis or dynamic causal modeling, will be needed to elucidate the directional nature of these relationships in future studies.

One hypothesis to explain behavioral and brain abnormalities in TS is that haploinsufficiency of genes on the X chromosome directly impacts fear recognition circuitry (Good et al., 2003;Zinn et al., 2008) and the frontoparietal network at large (Ziermans et al., 2012). Alternatively, decreased production of sex hormones in TS (Bakalov and Bondy, 2008;Hederstierna et al., 2009) may also affect fearful face processing regions and other limbic circuitry. In line with this hypothesis, dense distribution of estrogen receptors have been found in subcortical structures, including the basolateral amygdala (Osterlund et al., 2000). Also, previous studies demonstrating sexual dimorphism in prefrontal regions have attributed these differences to sex steroid hormone action (Goldstein et al., 2001) and evidence that genes on sex chromosomes are differentially expressed in the brain (Vawter et al., 2004) provide a further framework in which X-monosomy may significantly impact emotion processing circuitry. In total, these studies provide further insights into sexual dimorphism across a range of behavioral (Campbell et al., 2002;Kennedy and Adolphs,

2010;Montagne et al., 2005;Thayer and Johnsen, 2000), anatomical (Brooks-Gunn et al., 1987;Good et al., 2003) and functional (Kempton et al., 2009) emotion processing paradigms.

Although the results presented here contribute to a model linking X-monosomy with social-cognitive and neurobiological abnormalities, our ability to make definitive inferences is limited by several factors. For example, we did not collect eye-tracking data in this study. This would have been relevant given recent literature indicating that attention to the eye region is integral to disambiguating fearful stimuli (Gamer and Buchel, 2009). As women with TS primarily fixate on the mouth rather than the eyes when attending to emotional expressions of all valences (Mazzola et al., 2006), collection of eye-tracking data in future studies may shed further light on neural processes of fear recognition impairments. However, our findings when modeling only correct fear response trials suggest that even when attention is appropriately targeted to the stimulus, the underlying neurofunctional network for fear processing is aberrantly activated, implying that different attentional strategies do not solely account for these deficits in TS. Furthermore, given that fear recognition deficits in patients with amygdala lesions can be normalized when they are instructed to attend to the eyes (Adolphs et al., 2005;Kennedy and Adolphs, 2010), further investigation of the amygdala-adACC circuit and its relation to social cognitive deficits in TS is warranted. Similarly, acquisition of physiological data to assess fear arousal would have been useful to supplement our hypothesis of the role of the adACC in modulation of amygdala-driven affective response to fear.

We have presented data regarding the potential role of sex hormones in affect recognition, including the possibility that feminization of brain structures through circulating estrogen may influence certain aspects of the social cognitive neural network. While our results overlap in some aspects with a previous study of fear recognition in adults with TS (Skuse et al., 2005), there are also differences, notably a localization of effects in our study to the dorsal cognitive stream. While this may be mediated in part by paradigm selection, it may also represent developmental differences in emotional face processing circuitry. Given that nodes in this network undergo significant changes during adolescence, a better understanding of how these regions are influenced by sex steroids could result in improved clinical interventions. Therefore,

future directions of research in this area should include a longitudinal study observing changes in emotion processing across the pubertal period, with particular attention to the impact of dosing and administration of exogenous estrogen hormones in girls with TS. Furthermore, larger sample sizes across childhood and adolescence are required to fully appreciate age effects across development.

Conclusions

While many studies have examined aberrant fearful face processing, this is the first to do so in a population of young, prepubertal girls with TS. Here we demonstrate that young girls with TS show decreased accuracy in the recognition of fearful facial expressions. We also identify decreased function in the dorsal cognitive stream suggesting a mechanism that may underlie impairment in both emotional appraisal and regulation in TS. In particular, we note aberrant functional activation centered in the adACC, a region that integrates functions between the emotion and cognition networks. Studying how this circuitry is disrupted in TS provides the potential to examine genetic and hormonal influences on emotional face processing, as well as potential sexual dimorphic effects in this domain at large.

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Figure Captions:

Figure 1. Emotion recognition fMRI task design. Subjects were instructed to identify fearful, happy, and neutral facial expressions, and isoluminant scrambled images, by pressing a corresponding button. Stimuli were randomly ordered in a fixed sequence, with each condition being presented 30 times over the course of two separate scanning sessions. Stimuli duration was 1950ms, followed by a blank screen of 50ms. An additional 80 blank images consisting of a black background with a central fixation cross were pseudo-randomly interspersed throughout the entire task. Blank stimuli were 2000ms in duration, and no more than three blank screens were presented consecutively, resulting in an effective jittered interstimulus interval (ISI) ranging from 50-6050ms, with an average ISI of 2695ms.

Figure 2. Behavioral Accuracy and Response Times. (a) Repeated measures ANOVA of behavioral measures demonstrate a significant interaction effect of Group and Emotion. Post-hoc univariate analysis demonstrated that the TS group were less accurate in identifying fearful faces. (b) There were no significant Group x Emotion interactions for response times.

Figure 3: Analyses of between-group differences for contrast of happy faces compared to scrambled faces. The TS group demonstrated increased activation in the (a) right anterior fusiform gyrus ($p<.05$ corrected, peak: [57 -10 -27]). Analyses of between-group differences for contrast of fearful faces compared to scrambled faces. The TS group demonstrated decreased activation in the (b) right dorsolateral prefrontal cortex, and (c) right anterior cingulate and bilateral posterior cingulate gyri. Clusters are significant at $p<.05$ corrected for multiple comparisons.

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Table 1. Demographics and Cognitive Assessments

Independent t-test comparisons of demographics and WISC-IV index scores between TS and control groups.

	TS[a] (n=14)		Controls (n=16)		
	Mean	SD[b]	Mean	SD	p
Age	10.10	1.70	9.47	2.12	0.386
WISC-IV FSIQ[c]	90.43	12.74	117.38	7.56	<0.001
WISC-IV VCI[d]	105.14	15.22	117.69	14.25	0.028
WISC-IV PRI[e]	87.50	10.99	116.25	8.15	<0.001
WISC-IV WMI[f]	82.00	12.72	105.25	10.50	<0.001
WISC-IV PSI[g]	91.50	17.20	110.56	11.01	0.002

[a]Turner syndrome cohort; [b]Standard deviation; [c]Full Scale IQ; [d]Verbal Comprehension Index; [e]Perceptual Reasoning Index; [f]Working Memory Index; [g]Processing Speed Index

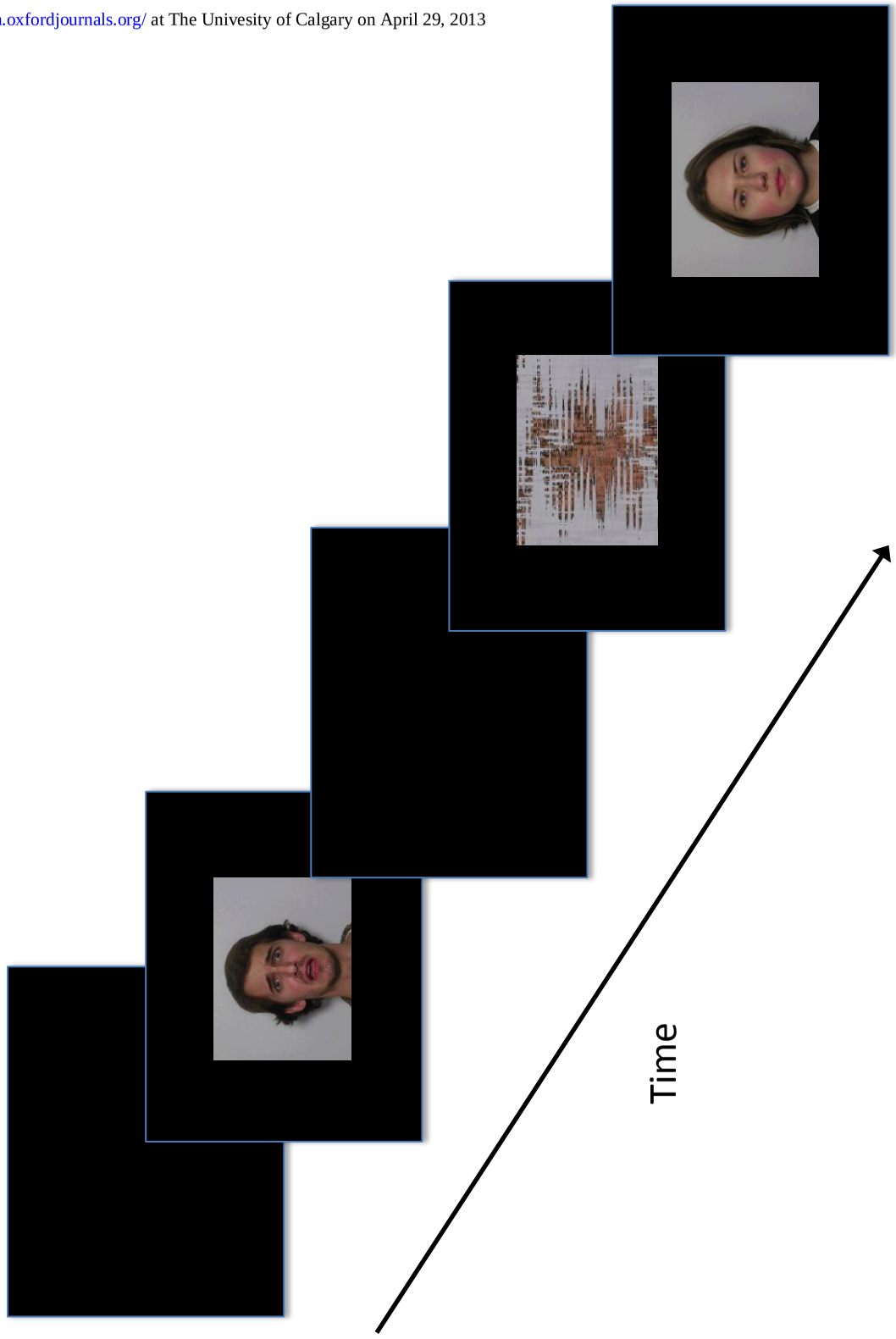
Table 2. Significant brain regions for within-group contrasts of emotional faces compared to scrambled faces at a whole-brain level. All clusters are p<.05 corrected for multiple comparisons and reported in Talaraich coordinates. Voxel size is 1.5mm^3.

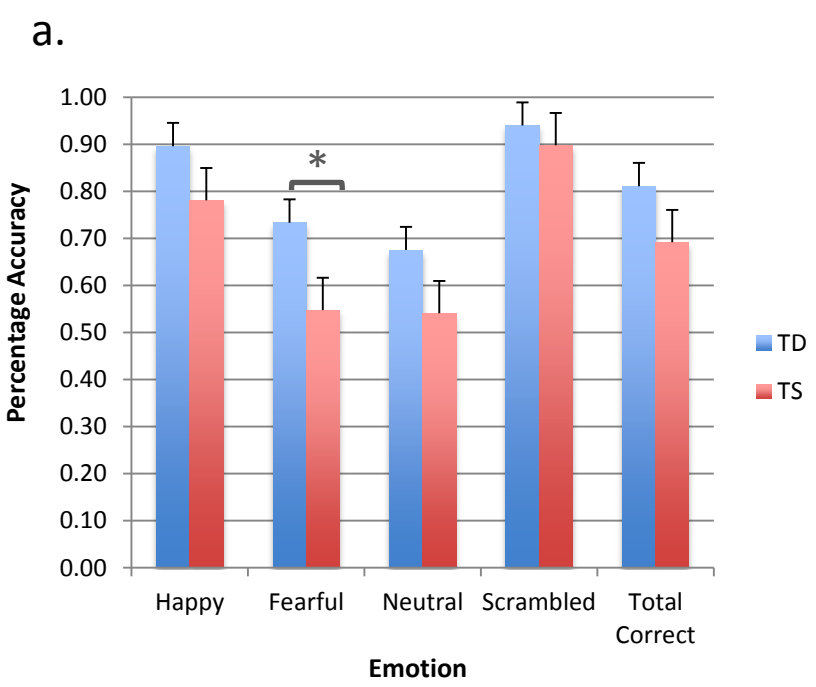
	Happy>Scrambled		**Talaraich Peak Coordinates**				
	Regions	**BA**	**x**	**y**	**z**	**T**	**# of Voxels**
TD	R Amygdala		21	-12	-12	6.77	337
	R Caudate	9	10	11	8		371
	R Middle temporal gyrus	39	46	-63	25	4.74	322
	R Superior temporal gyrus	41	46	-33	9	4.45	282
	R Insula	13	46	-41	17	4.42	
TS	L Fusiform gyrus	36	-31	-4	-28	7.38	243
	L Superior temporal gyrus	38	-34	19	-31	5.77	
	L Inferior temporal gyrus	20	-36	1	-33	5.75	
	R Fusiform gyrus	20	34	-10	-26	6.85	1437
	--	37	42	-41	-13	5.58	247
	R Amygdala		28	-8	-10	6.34	
	--		33	-7	-17	6.22	
	R Superior temporal gyrus	38	43	12	-31	6.55	762
	L Posterior cingulate gyrus	23	0	-44	24	6.06	864
	--	29	-1	-40	10	4.14	
	R Middle occipital gyrus	19	46	-80	3	5.92	697
	R Middle temporal gyrus	39	45	-71	15	4.92	
	--	39	40	-66	25	4.76	

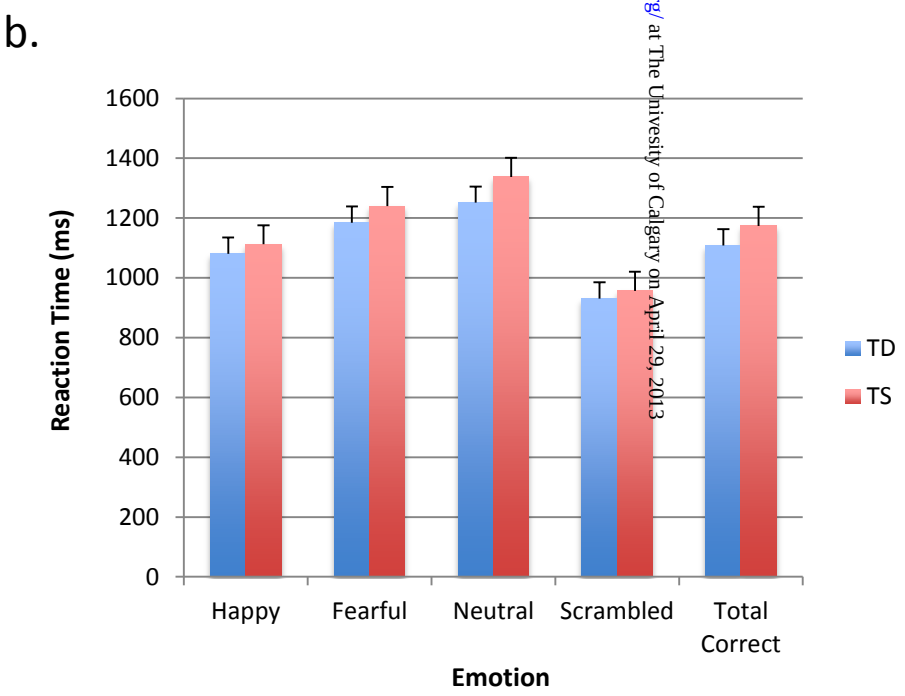
	Fearful>Scrambled		Talaraich Peak Coordinates				
	Regions	**BA**	**x**	**y**	**z**	**T**	**# of Voxels**
TD	R Inferior frontal gyrus	45	52	25	6	9.74	4673
	R Anterior fusiform gyrus	9	45	18	38	5.60	
	L Inferior frontal gyrus	45	-56	21	7	9.16	3569
	L Insula	13	-39	22	9	7.02	
	R Fusiform gyrus	37	40	-46	-14	8.89	423
	L Middle frontal gyrus	9	-37	18	31	6.57	1157
	L Anterior fusiform gyrus	9	-37	6	40	5.44	
	R Parahippocampal gyrus	21	34	-3	-26	5.81	1216
	R Amygdala		25	-6	-11	5.53	
	R Inferior temporal gyrus	20	36	-5	-34	5.03	
	R Middle temporal gyrus	19	53	-63	17	5.74	1423
	R Superior temporal sulcus/Temporoparietal junction	39	46	-66	17	5.33	
	R Middle occipital gyrus	18	40	-86	1	5.12	
	R Anterior cingulate gyrus	32	7	28	29	5.37	1813
	L Superior frontal gyrus	8	0	27	51	4.82	
	R Superior frontal gyrus	6	7	22	54	4.76	
	L Fusiform gyrus	18	-46	-82	-1	3.91	273
	--	19	-46	-75	7	5.27	
TS	R Inferior temporal gyrus	21	40	-7	-30	6.31	243
	R Amygdala		27	-4	-15	4.96	
	R Superior temporal gyrus	38	45	10	-26	4.65	
	L Fusiform gyrus	20	-37	-11	-26	5.67	241
	R Fusiform gyrus	37	42	-41	-13	5.44	243
	--	20	45	-30	-20	4.29	

	R Inferior frontal gyrus	44	56	17	16	5.02	257

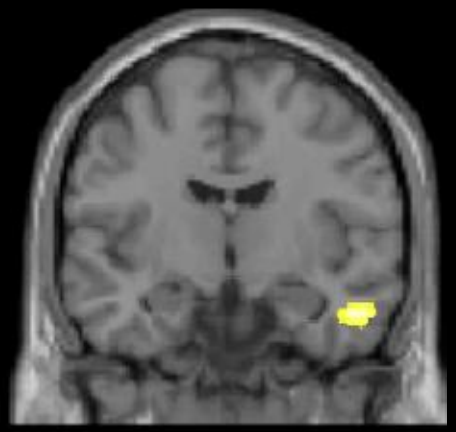
BA = Brodmann area; T = T-score of peak coordinates; TD = Typically developing cohort; TS = Turner syndrome cohort; R = Right; L = Left







a.



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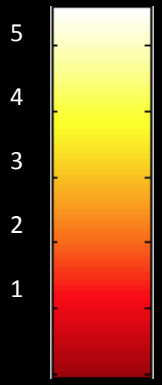
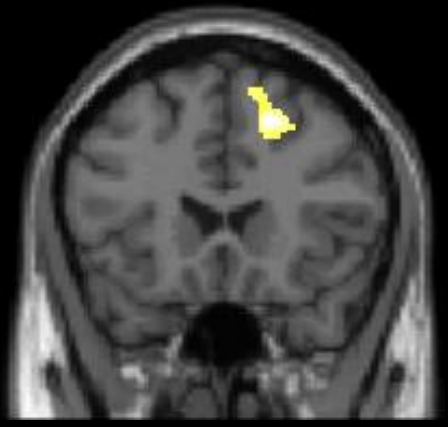
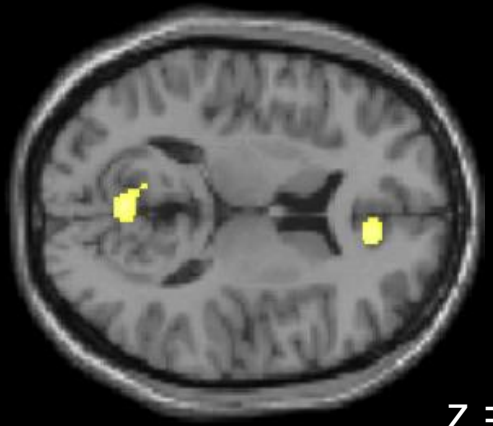


b.



y = 22

c.



z = 13