Functional dissociation of amygdala-modulated arousal and cognitive appraisal, in Turner syndrome

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The amygdala is preferentially activated by facial expressions of fear. Right and left amygdala are hypothesized to play distinct, but complementary, roles that influence somatic and cognitive responses to facial expressions. Right amygdala activation is linked to autonomic arousal, and thus indirectly influences left hemisphere cognitive processing centres. Left amygdala activation is more closely associated with cognitive processing and differentiation of facial emotions. A double-dissociation between the functions of left and right amygdala is implied by lesion studies but supportive evidence is inconsistent, partly because patients with structural antero-medial temporal anomalies have experienced variable surgical procedures. A functional dissociation can be demonstrated between arousal and the cognitive appraisal of fearful faces in the condition of X-monosomy or Turner syndrome. Previous research found Turner syndrome women of normal verbal intelligence are seriously impaired in their ability cognitively to differentiate fearful from other facial expressions but they acquire fear conditioning normally, with enhanced autonomic responses. These findings supported the dissociation hypothesis, which was formally tested in a study of 12 X-monosomic and 12 control females who participated in functional magnetic resonance imaging during which simultaneous skin conductance recordings were acquired. Faces depicting fear or neutral emotions were presented to both case and control subjects in random order. Arousal to (fearful–neutral) faces was associated with transiently increased skin conductance responses and bilateral amygdala activation in both groups, but X-monosomic females had proportionately greater—and more persistent—right amygdala activation than controls. In both groups, cognitive accuracy correlated positively with differential activity of left fusiform gyrus. There was a significant correlation between the left fusiform and left medial amygdala activation only in normal females, and only in them did differential SCRs (to fearful–neutral faces) correlate positively with left fusiform responses. Arousal and cognitive appraisal functions of the amygdala can thus be functionally dissociated. X-monosomy selectively impairs explicit recognition of fearful faces in the presence of normal or enhanced autonomic reactivity, and is associated with a functional dissociation of activity in left amygdala and left fusiform gyrus. These findings imply X-linked genes are essential for binding somatic responses to the cognitive appraisal of emotional stimuli.

Introduction

Facial expressions are important social signals and provide critical information about potentially salient environmental cues. Certain expressions signal threat, and these expressions are associated with distinct neural substrates (Anderson *et al.*, 2003). The amygdala is preferentially activated in response to facial expressions of fear, compared with other facial expressions, such as neutral or happy (see Zald, 2003 for review) and comprises a critical component of the neural

system for evaluating such expressions, probably because they might indicate an imminent threat (Dolan and Vuilleumier, 2003). The amygdala plays a critical role in fear conditioning, which is a variant of Pavlovian classical conditioning (see LeDoux, 1998). The conditioned stimulus in a fear-conditioning experiment with humans might involve a loud noise (the unconditioned stimulus), a negative facial expression (the conditioned stimulus) and an autonomic response such as an increased skin conductance (the conditioned response). Conditioned fear learning occurs very quickly in normal people, and it can result in persistent associations. On the other hand, repeated exposure to the conditioned stimulus in the absence of the unconditioned stimulus usually leads to 'extinction', and the conditioned response 'habituates' and diminishes in magnitude.

Fearful faces are often considered to be processed automatically and independent of attention (Vuilleumier *et al.*, 2001, 2002; Williams *et al.*, 2005*a*) and awareness (Esteves *et al.*, 1994; Anderson *et al.*, 2003; Pasley *et al.*, 2004), although contrary evidence has been reported by one group (Pessoa *et al.*, 2002). The intensity of the affective response (measured by autonomic arousal) is directly related to the magnitude of amygdala activation (Anderson and Sobel, 2003); the amygdala participates in autonomic activity, such as skin conductance responses (SCRs) (Lang *et al.*, 1993; Furmark *et al.*, 1997; Critchley *et al.*, 2002; Sah *et al.*, 2003). Efferent projections from the central nucleus include pathways to brainstem regions controlling motor and visceromotor responses and hypothalamic areas that control hormonal release (Davis, 1997). Co-activation of amygdala and arousal systems is thought to enable the cortex to distinguish fear signals from other arousal responses to novel stimuli (Damasio, 2000). Humans with bilateral amygdala lesions are still able to generate an SCR to certain stimuli, but its magnitude is diminished (Tranel and Damasio, 1989; Masaoka *et al.*, 2003). They are not only impaired in their physiological responses, but also in their cognitive evaluation of an arousing emotional stimulus, such as a fearful face (Adolphs *et al.*, 1994; Young *et al.*, 1995; Calder *et al.*, 1996; Broks *et al.*, 1998; Anderson and Phelps, 2000). However, left and right amygdala play distinct, but complementary, roles in the somatic and cognitive response to facial expressions. Damage to the left amygdala leaves autonomic responses intact, but is associated with a severe cognitive deficit (Glascher and Adolphs, 2003). Damage to the right amygdala can lead to autonomic arousal impairment, with a modest influence on cognitive evaluation. Thus, one interesting view is that the cognitive appraisal of negative facial expressions by the left amygdala appears to be enhanced by concomitant somatic arousal, as measured by SCR (Glascher and Adolphs, 2003; Williams *et al.*, 2005*b*). The right amygdala serves to facilitate the cognitively mediated recognition of negative emotions by the left amygdala (Morris *et al.*, 1997; Phillips *et al.*, 1998; Dubois *et al.*, 1999; Lane *et al.*, 1999).

The above hypothesis would fit in with evidence that the right amygdala is generally responsive to arousing stimuli (e.g. facial expressions), independent of their valence (Williams *et al.*, 2004*b*). Left and right amygdala may work in concert, to produce an orchestrated behavioural response to threat, which guides cognition and behaviour (Hariri *et al.*, 2003). An intact (right-amygdala mediated) autonomic response enhances cognitive evaluation, but is neither sufficient nor necessary for accurate appraisal of a threatening stimulus (Glascher and Adolphs 2003; Hariri *et al.*, 2003). Preserved cognitive evaluation requires efferent and afferent connectivity between the left amygdala and cortical regions associated with face processing, such as the fusiform gyrus (Kanwisher, 2000). Accordingly, the physiological and cognitive correlates of amygdala activity to visual presentation of emotional facial cues might be doubly dissociated, the dissociation being critically linked to the relatively distinct functions and properties of the human left and right amygdalae.

While a dissociation between has been hinted at in previous literature, the interpretation of findings has been complicated by the fact that all subjects have had extensive damage to the amygdala, usually as a result of surgery for intractable epilepsy, which often impacts on other medial temporal structures such as the hippocampus. These regions are also reported as responsive to negative facial emotions (Surguladze *et al.*, 2003). There are no previous reports of an intact autonomic response to facial expressions of fear, in the absence of accurate cognitive evaluation, other than in instances of physical damage to the amygdala. The main aim of this investigation was to test the hypothesis that the autonomic and cognitive functions of the amygdala could be dissociated in X-monosomic females, in whom brain structure is essentially normal.

The chromosomal disorder Turner syndrome (X-monosomy, 45,X) provides a model system in which the form and severity of deficits in the cognitive appraisal of facial expressions and social emotions are virtually identical to those seen in bilateral amygdalectomy patients (Lawrence *et al.*, 2003*a*, *b*). There is additional evidence, from voxel-based morphometry, of structural amygdala anomalies in this condition, grey matter density being increased relative to normal females (Good *et al.*, 2003).

To test the integrity of amygdala-related functions in Turner syndrome we conducted a behavioural study of fear conditioning, in which angry faces were used as the conditioned stimulus, an aversive loud sound as the unconditioned stimulus (Morris and Dolan, 2004) and SCRs were recorded. These behavioural data (unpublished) indicated that females with Turner syndrome showed normal acquisition of fear conditioning, suggesting that in this respect they had normal amygdala function (LeDoux, 1998). Patients with bilateral amygdala lesions have impaired explicit appraisal of fearful facial expressions too, but their autonomic responsiveness is also impaired to the conditioned stimuli in a fear conditioning experiment (Bechara *et al.*, 1995). Accordingly, we had *a priori* evidence to support a hypothesis for a double dissociation between cognitive and physiological functions of the amygdala and their related circuitry.

This investigation aimed to test three predictions. Firstly, X-monosomic females would be impaired, relative to normal females, in their recognition of fearful faces. Secondly, right amygdala activity would be correlated with autonomic arousal as measured by SCR in both subject groups, and could be enhanced in the X-monosomic sample. Thirdly, fearful face recognition in both Turner syndrome and normal females would be correlated with activation of inferior fusiform cortex.

Methods
Subjects
Twelve females with Turner syndrome were selected from a database we have established of participants who have contributed to previous research on this condition. Criteria for selection included: monosomy for an X-chromosome of maternal origin, no detectable mosaicism for non-monosomic cell lines (Jacobs *et al.*, 1997); no known neurological anomalies; no history of epilepsy. The choice of 45,X females, whose single X-chromosome was maternally derived, was based on behavioural data indicating that those with a single paternal X-chromosome had better social adjustment (Skuse *et al.*, 1997). Accordingly, we aimed to reduce variance on key variables that may have confounded interpretation of the findings. Mean age was 27.25 years (SD 4.1); mean verbal intelligence quotient (IQ) 99.2 (SD 12.1), mean non-verbal IQ 91.1 (SD 16.1). None had been referred because of behavioural or cognitive difficulties: ascertainment was usually in childhood on the grounds of short stature or failure to develop secondary sexual characteristics. All were taking oestrogen replacement at the time of study (mean age of commencement was 15 years). Performance on emotion recognition from facial expressions was established prior to scanning using standard procedures (Ekman and Friesen, 1976). Subjects viewed 60 faces (10 for each of the six 'basic' emotions in random order), and indicated whether the emotion being expressed was happy, sad, fearful, angry, disgusted or surprised. The number of correct identifications of fearful faces (on a 0–10 scale) was used as an index of explicit fear recognition.

We selected 12 normal females from a database of control participants (mean age 25.6 years (SD 4.6); mean verbal IQ 103.7; SD 14.8, mean non-verbal IQ 109.9; SD 11.8). All were right-handed and had no history of psychiatric or neurological disorder. There was a significant difference between the performance IQ of the Turner syndrome sample ($P < 0.001$) and that of the normal females, but no significant difference in terms of verbal IQ. We established performance on the standard facial expression recognition task prior to scanning.

Stimuli and experimental design
Grayscale images of fearful and neutral expressions from six different individuals (three male and three female) were taken from a standard set of pictures of facial affect (Ekman and Friesen, 1976). During scanning, subjects viewed the different face stimuli (all $6.6 \times 4.4°$ in size) projected singly for 500 ms onto a screen placed above the head volume coil of the functional magnetic resonance imaging (fMRI) scanner. The interstimulus interval was 6 s, and the participants viewed a fixation cross during this period. Each of the six faces in the fearful/neutral conditions was shown four times. Condition order was randomized. Subjects' explicit task was to decide the sex of each face, making responses by right hand button presses. The duration of data capture was ~600 s.

Data acquisition
Neuroimaging data were acquired with a 2 T Magnetom VISION whole body MRI system (Siemens, Erlangen, Germany) equipped with a head volume coil. Contiguous multi-slice T2* weighted echo-planar images were obtained using a sequence that enhanced blood oxygenation level dependent (BOLD) contrast. Volumes (33 slices, slice thickness 2 mm) were acquired continuously every 2.5 s. A T1 weighted anatomical MRI was also acquired for each subject.

Changes in skin conductance were measured during scanning as an index of implicit emotional responses. SCRs were monitored with Biodata galvanic skin response equipment using Ag/AgCl electrodes attached to the palmar surface of the middle phalanges of the index and middle fingers of the left hand. Readings of skin conductance were sampled at 100 Hz and stored digitally on computer. Using the SCR in the 4 s period prior to stimulus presentation as a baseline, the maximal SCR deflection in the period 0.5–4 s following a face-presentation was assigned as the event-related SCR to that face. Mean SCRs were calculated for fearful and neutral conditions, and mean differential fear responses (i.e. mean fear–mean neutral) for each subject were used as an implicit response variable.

Data analysis
The fMRI data were analysed using statistical parametric mapping with SPM99 (http://www.fil.ion.ucl.ac.uk/spm). Following realignment to the first volume, the functional (T2* weighted) scans were spatially normalized into a standard stereotaxic space, based on a 152 subject average brain image supplied by the Montreal Neurological Institute. The functional data were smoothed using a 6 mm (full width at half maximum) isotropic Gaussian kernel to allow for corrected statistical inference. The evoked haemodynamic responses for the different stimulus events were modelled as delta functions convolved with a synthetic haemodynamic response function and its temporal derivative.

Subject-specific parameter estimates were calculated for each event type at every voxel. Specific effects were tested by applying linear contrasts to the parameter estimates for each event (fearful–neutral). Contrast images from each subject were entered into second-level (random effects) analyses using explicit (recognition) and implicit (SCR) response variables as regressors. Reported *P* values are corrected for the number of comparisons made within each *a priori* region of interest, i.e. amygdala and fusiform gyrus. Regions of interest were defined as spheres with radii of 8 mm for amygdala, and 10 mm for fusiform gyrus centered on previously reported fear-related activations (Morris *et al.*, 1996, 2001). Time by event interaction analyses were performed by multiplying the regressors for the stimulus events, with a mean corrected exponential function having a time constant one quarter the session length.

In a separate analysis of the neuroimaging data, we tested for 'psychophysiological interactions' (PPIs), i.e. condition-dependent changes in the covariation of response between amygdala and other brain regions (Friston *et al.*, 1997). Using a specially developed routine in SPM, the adjusted data in each session were first deconvolved, and the region of maximal amygdala activity at the time of the fearful face trials extracted. The resulting condition-specific estimate of neuronal activity was then reconvolved with a synthetic haemodynamic response function. This procedure was repeated for

the neutral trials. The resulting regressors were entered as variables of interest into separate analyses. Linear contrasts were applied to the parameter estimates for the regressors in order to identify other brain regions where responses exhibited significant condition-dependent interactions with amygdala activity.

Results
Cognitive evaluation of facial expressions
Turner syndrome females were significantly impaired in explicit recognition of fearful facial expressions compared

to normal control females, as anticipated (Lawrence *et al.*, 2003*b*). The full Ekman-Friesen set of emotional faces computes accuracy as a proportion of scores/10 for each facial expression. X-monosomic and comparison females' performance on a test of face emotion recognition (six emotions) is summarized in Fig. 1A. A multivariate analysis of covariance was used to test for a difference between the groups in their ability to recognize facial expressions of emotion. Accuracy scores (out of 10) for each facial expression category were entered as the dependent variables, with group as the fixed factor and performance IQ as a covariate. Facial expressions of
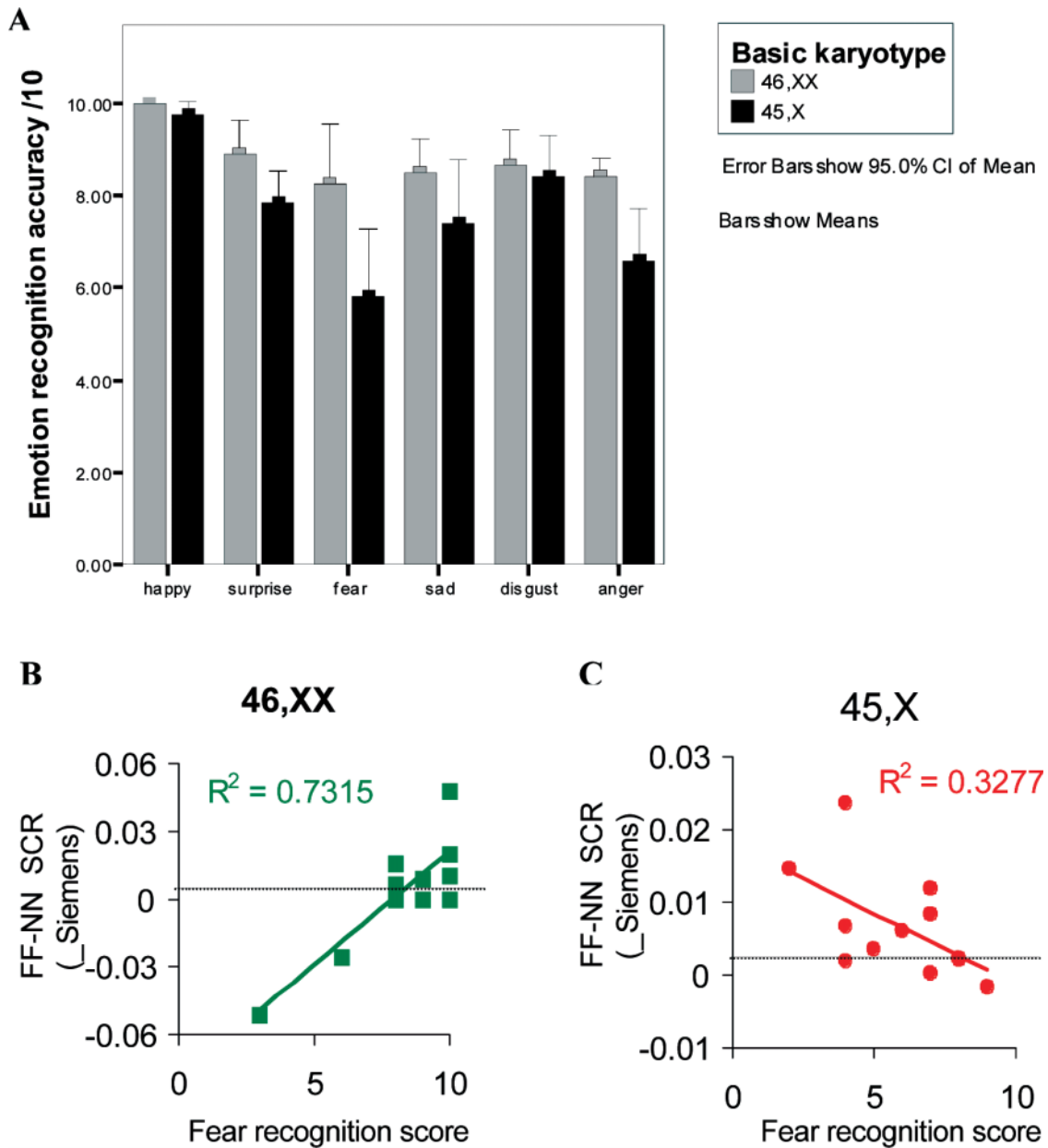

Fig. 1 Cognitive performance of case and comparison samples in face emotion recognition. (**A**) Bar chart showing performance in terms of accuracy of emotion recognition for six standard emotions: significant differences between groups are only found for fear and anger, with X-monosomic females performing less well than normal 46,XX females. (**B** and **C**) Scatter plots for case and comparison subjects. SCR averaged across testing session for (fearful–neutral) faces is plotted against the cognitive performance score on the fear-emotion recognition task (scores/10).

fear [$F(1, 21) = 7.20$, $P = 0.01$] and anger [$F(1, 21) = 8.28$, $P = 0.009$] were recognized significantly less accurately by women with Turner syndrome than by control females. Recognition accuracy for happiness, sadness, disgust and surprise did not differ among the groups. The impact of non-verbal IQ upon the ability to perform this task was non-significant in both groups. The fact that the significance of the difference was not reduced when assessed by an analysis of covariance, in which performance IQ was the covariate, is consistent with our previous research (Lawrence *et al.*, 2003*a*). Errors made by each group with regard to the recognition of fear differed substantially. In general, failure to recognize a fearful face as depicting fear was usually associated with the misattribution of the emotion as surprise. Responding with 'surprise' accounted for a higher proportion of the fear errors for the control females (90%) than for the women with Turner syndrome (64%) (statistically non-significant with samples of this size). Errors for the women with Turner syndrome were more diverse and they reported fearful faces to look disgusted, angry, sad and even happy. The only error, other than surprise, made by the control women was to misattribute the emotion disgust to fearful faces.

Arousal—SCRs

In normal female subjects, SCRs were enhanced to fearful faces relative to neutral faces, although the difference showed only a trend towards statistical significance when averaged across the testing session: (mean fearful compared with neutral faces: mean fearful–neutral SCR = 3.0 mSi; $P = 0.3$). In contrast, Turner syndrome subjects exhibited significantly enhanced differential SCRs to fearful faces, averaged across the entire session ($\sim$10 min). Mean (fearful–neutral) faces SCR = 6.57 mSi; $P < 0.01$. While the group difference between Turner syndrome and control females was large, there was substantial intra-group variance and that difference did not reach statistical significance. In Fig. 1B and C we show the relationship between SCR and explicit performance on the task of fearful-face recognition for both normal and X-monosomic females, demonstrating the dissociation in the latter sample between arousal (averaged across the experiment) and performance on the explicit task.

Normal female subjects showed enhanced SCRs to fearful faces in the early stages of the scanning session (i.e. in the first 3 min), but these rapidly habituated in the remainder of the session. The lack of significant differential SCRs, averaged across the session, in the fearful/neutral face contrast is largely attributable to this rapid habituation.

Arousal—amygdala BOLD response

We first identified brain regions engaged in processing fearful stimuli by determining increased differential BOLD fMRI responses to fearful faces relative to neutral, using a whole brain voxel by voxel analysis. Turner syndrome and normal female subjects both showed increased bilateral amygdala responses to fearful faces, but the magnitude of the responses differed by group. A test of the group by condition interaction, i.e. (45,X–46,XX) by (fearful–neutral) mean BOLD responses, showed that Turner syndrome females had significantly enhanced ($P < 0.01$, corrected) right amygdala responses (maximal voxel: $x = 28$, $y = -4$, $z = -24$, $P < 0.01$, corrected) to fearful faces compared to controls. There were no significant differences between the groups in the differential activity of the left amygdala response to (fearful–neutral) faces.

In a separate analysis of the neuroimaging data, subject-specific SCRs to fearful faces were used as a covariate of interest to identify neural activity that correlated with stimulus-evoked autonomic responses using a whole brain correlation analysis. Separate analyses were done for each group. In keeping with our prediction that arousal would be normal or enhanced in the Turner sample, and would be most closely correlated with activity of the right amygdala, we found in both Turner syndrome and, independently, in normal female subjects, fear evoked SCRs (as summarized in Fig. 1) correlated positively with right amygdala responses (maxima: $x = 24$, $y = -8$, $z = -16$, $P < 0.01$, corrected), as predicted (R^2 for controls was 0.62, $P < 0.01$ and that for 45,X was 0.76, $P < 0.01$). The correlation between left amygdala activation and arousal was similar in both groups (maxima: $x = -18$, $y = -10$, $z = -20$) (R^2 for cases was 0.63, $P < 0.01$ and R^2 for controls was also 0.63, $P < 0.01$).

Time-dependent changes in BOLD response

In view of the importance of time-dependent changes in neural responses to fearful stimuli, especially in amygdala (Breiter *et al.*, 1996; Buchel *et al.*, 1998), we conducted further analyses to identify time-dependent changes in differential neural responses to fearful faces. In normal female subjects, fearful faces initially evoked increased bilateral amygdala responses that progressively decreased across the experimental session (maximal voxels: right $x = 26$, $y = 2$, $z = -20$, $P < 0.01$, corrected; left $x = -14$, $y = -2$, $z = -22$, $P < 0.01$, corrected). In contrast, in women with Turner syndrome there was no consistent pattern of decrease. A significant group (46,XX–45,X) by condition (fearful–neutral) BOLD responses by time (exponentially decreasing course of activation) interaction was identified in bilateral amygdala (maximal voxels: right $x = 22$, $y = 4$, $z = -22$, $P < 0.01$, corrected; left $x = -22$, $y = -2$, $z = -22$, $P < 0.01$, corrected). This result, indicating differing patterns of activation that were more sustained in the X-monosomic females, is illustrated in Figs 2 and 3. Figure 2 presents data relevant to the right amygdala in a two-dimensional form, in which the peristimulus response pattern has been averaged across the experiment. In contrast, Fig. 3 presents data for the left amygdala in a three-dimensional form, in which the pattern of left amygdala response can be seen for the entire duration of the experiment.
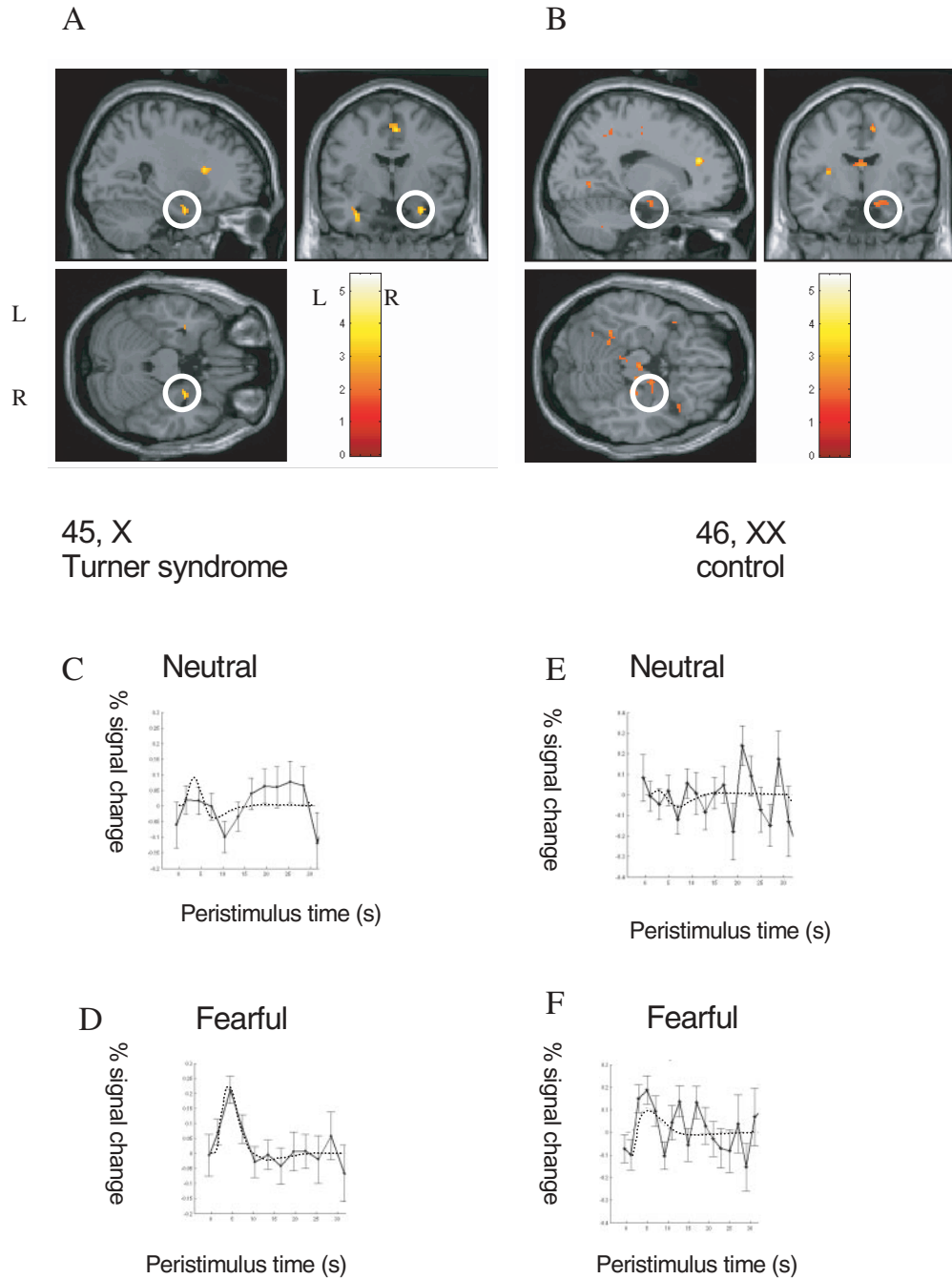
A

B

45, X
Turner syndrome

46, XX
control

C   Neutral

% signal change

Peristimulus time (s)

E   Neutral

% signal change

Peristimulus time (s)

D   Fearful

% signal change

Peristimulus time (s)

F   Fearful

% signal change

Peristimulus time (s)

Fig. 2 Amygdala response to fearful faces. SPM images displaying a region of right amygdala (maximal voxel: $x = 24$, $y = -8$, $z = -16$, $P < 0.01$, corrected) where activation showed a positive correlation with SCR response to prototypical fearful faces in both Turner syndrome subjects (**A**) and normal controls (**B**). (**C** to **F**) Peristimulus time histograms (with 2 second bins) displaying mean BOLD fMRI responses in maximal right amygdala voxel to neutral and fearful face stimuli, for normal (46,XX) females (Figures 2E and 2F) and Turner syndrome (45,X) females (Figures 2C and 2D). These data are displayed with a peristimulus time scale of 30 seconds following presentation of the relevant image. Standard error bars are superimposed. Dotted lines give mean group values averaged across the (600 s) session for 30-second intervals; inspection of these lines shows that patterns of activation are similar for both groups in response to neutral faces (Figures 2B and 2D). There are however marked differences in the pattern of right amygdala activation to fearful faces. Turner females show a rapid and persistent response throughout the experiment (Figure 2D) but the magnitude of response—averaged across the experiment—is clearly lower in the comparisons (Figure 2F).

Figures 2A and 2B show the region of right amygdala consistently activated by exposure to fearful-neutral faces in X-monosomic subjects, and normal females respectively ($x = 24$, $y = -8$, $z = -16$). The focus on the right amygdala in

this analysis is motivated by its known association with SCR. Figures 2C–2F show peristimulus time histograms with 2 second bins, sampling a period of 30 seconds, and representing the averaged activity of the right amygdala signal
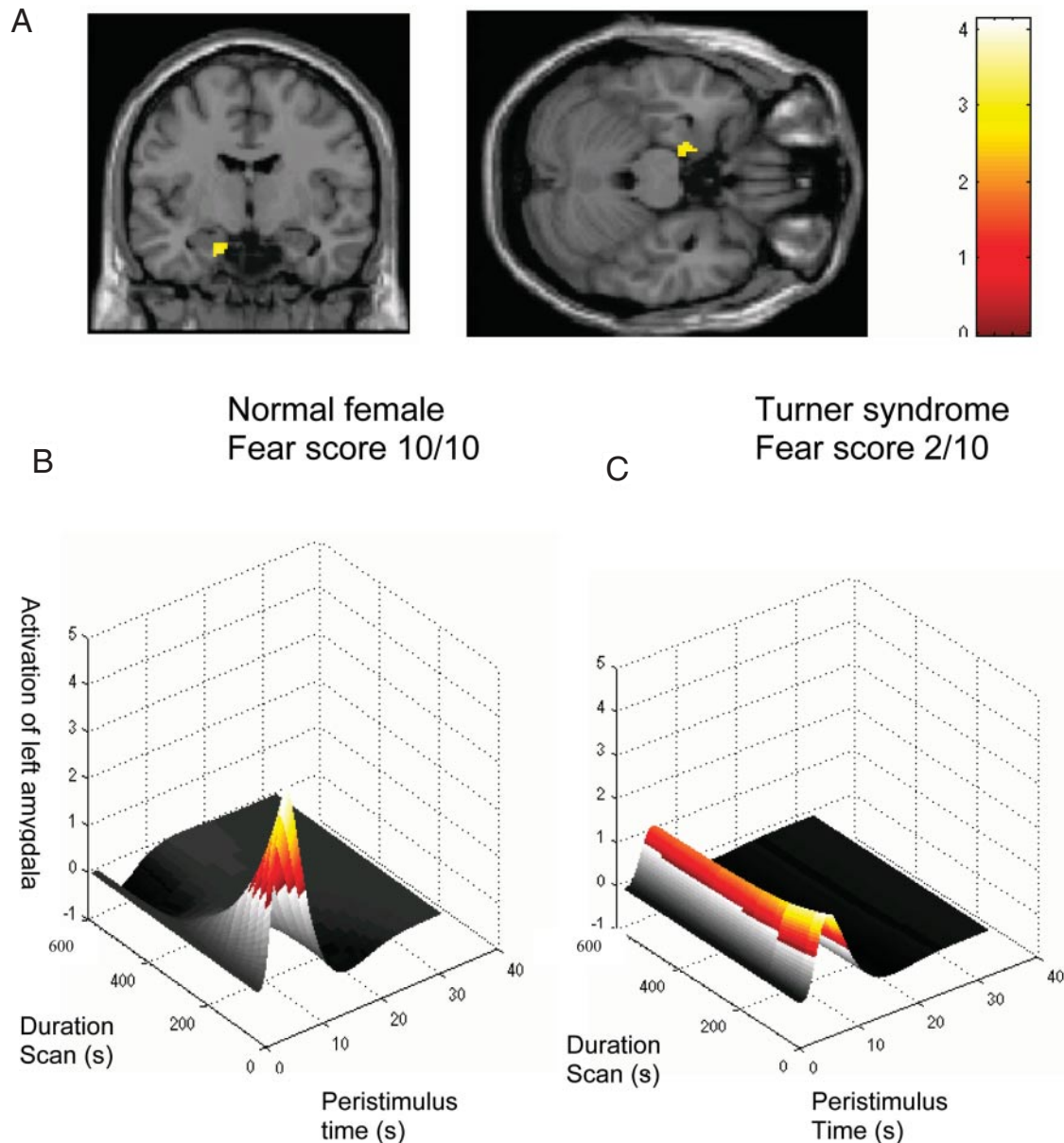
Fig. 3 Time-dependent changes in left amygdala responses to fearful faces. (**A**) SPM figure displaying region of left amygdala which showed, in a group (46,XX–45,X) by condition (fearful–neutral faces) by time (exponentially decreasing course of activation) interaction, significantly different patterns of activation in Turner syndrome compared to normal females ($x = -22$, $y = -2$, $z = -22$, $P < 0.01$). Three-dimensional plots of time-dependent changes in BOLD fMRI responses in maximal left amygdala voxel to prototypical fearful faces are shown for representative normal female (46,XX) (**B**) and Turner syndrome (45,X) (**C**) subjects. The peristimulus time is similar in both plots, but the magnitude of the left amygdala activation is substantially greater in the early phase of the scan in normal females and then rapidly reduces, whereas the left amygdala of the sample 45,X female shows a persisting pattern of activation, which varies little in magnitude during the course of the experiment.

change to neutral (2C, 2E) or fearful (2D, 2F) faces across the entire testing session. The patterns of signal change in the two groups to neutral faces (2C-45,X,2E-normal females) indicate that the standard error bars for mean response are larger for the controls than cases, especially toward the end of the 30-second sampling window, but the mean pattern of response (indicated by the dotted line) does not differ statistically significantly. In contrast, consider the peristimulus time pattern for the presentation of fearful faces (2D-45, X,

2F—normal females). Averaged across the entire session there are differing patterns of response. Both groups show an initial activation in the first 5–10 seconds, but the magnitude of this response is consistently increased throughtout the session for the Turner syndrome females.

In Fig. 3 the pattern of change in the BOLD response over time is explored, using a three-dimensional analysis with a focus on the left amygdala. Changes in the BOLD fMRI response are given (Fig. 3B and C), for an individual voxel,

showing maximal response to prototypical fearful faces (in both examples). The voxel in question (at $x = -14$, $y = -2$, $z = -22$) is within the area activated by the contrast (fear–neutral) in Fig. 3A. Examples are given of two representative subjects, one a normal female with a perfect fear recognition score (Fig. 3B) and the equivalent data for a Turner syndrome female with poor fear recognition skills (Fig. 3C). In the normal female there is a rapid but transient activation of the left amygdala, with a peristimulus time of 5–10 s, but the magnitude of this activation rapidly diminishes during the course of the experiment. In contrast, the Turner syndrome female shows a less marked peak at the outset, but continues to respond to fearful faces throughout the session with a similar peristimulus time pattern (shown as the axis 'peristimulus time'). The equivalent picture, in respect of the right amygdala and presented two-dimensionally, is shown in Fig. 2D.

Cognitive performance—SCRs

There was a substantial positive correlation between fear recognition performance and mean fearful–neutral SCR in the normal females, of 0.85 ($P < 0.01$), indicating that the greater the somatic correlates of arousal in normal females the better their performance on the cognitive appraisal task (Fig. 1B). Of course, we do not know the direction of effect, but there is at least a possibility that the cognitive appraisal was enhanced by autonomic influences. Within the normal female sample only 2/12 subjects showed a mean negative SCR response (fearful–neutral) during the course of the session, and both obtained relatively poor fear recognition scores (≤ 6). This observation was in striking contrast to the SCR correlates of poor fear recognition in the Turner syndrome sample. In this group, the net SCR was positive in 11/12 subjects, but 6/12 obtained fear scores that were ≤ 6. In complete contrast to the controls, Turner syndrome women with the greatest net mean change in SCR during the course of the experiment tended to have lower accuracy in the cognitive task, and the correlation was negative ($r = -57$, $P < 0.01$), (Fig. 1C).

Fear recognition performance—BOLD response

Mean bilateral amygdala responses to fearful faces covaried positively with fear recognition scores in normal female subjects (maximal voxels: right $x = 26$, $y = -4$, $z = -24$, $P < 0.01$, corrected; left $x = -20$, $y = -10$, $z = -20$, $P < 0.01$, corrected), indicating both amygdala contributed to correct performance (for the correlation between fear recognition and left amygdala activation (fear–neutral) $R^2 = 0.51$, $P < 0.01$; right amygdala activation correlation $R^2 = 0.52$, $P < 0.01$). In contrast the correlation between performance and activation of left amygdala in the Turner syndrome females was non-significant ($R^2 = 0.12$, $P = $ n.s.), and the correlation with right amygdala activation was negative ($R = -0.86$, $P < 0.01$).

To identify brain responses associated with cognitive processing of fearful faces, subject-specific scores on fearful expression recognition were used as a covariate of interest in a further analysis of the neuroimaging data. In effect, we correlated fear recognition scores with the magnitude of activation for the contrast of fearful-neutral over the entire brain. Previous studies have found relatively greater activation in bilateral extrastriate cortex to fearful compared with neutral faces, especially within the fusiform gyrus (Morris *et al.*, 1998). This is a region closely associated with the processing of social information from faces (Kanwisher *et al.*, 1997). We found a positive correlation between the activity of a voxel of maximal responsiveness to faces in the left fusiform gyrus of both groups and their fear recognition ability. Left fusiform activity (fearful–neutral faces) co-varied positively with fear recognition scores in both Turner syndrome ($r = 0.81$; maximal fusiform voxel: $x = -36$, $y = -58$, $z = -12$, $P < 0.05$, corrected) and normal female subjects ($r = 0.6$; maximal fusiform voxel: $x = -30$, $y = -60$, $z = -16$, $P < 0.05$, corrected). A common activation of left fusiform gyrus by fearful faces, in relation to fear recognition score, was also tested in a conjunction analysis of the separate group-specific contrasts and by inclusive masking of the 45,X regression with the 46,XX regression contrast (maximal voxel: $x = -34$, $y = -60$, $z = -14$, $P < 0.01$, corrected). This implies that in both the X-monosomic and the normal females activation of left fusiform gyrus is crucial to accurate recognition of fearful faces in the explicit task; there was no group difference in the interpretation of these data. In contrast, the right fusiform activation correlations with cognitive performance did not reach a corrected level of significance for either group.

Neocortical sensory processing of emotionally salient stimuli may be enhanced by feedback connections (Glascher and Adolphs, 2003), therefore we investigated the covariation of fusiform responses to fearful faces with fear-evoked SCRs. SCRs to fearful faces (mean change fear-neutral faces as Fig. 1B and C) correlated positively with left fusiform responses in normal females, as predicted ($r = 0.66$ at maxima: $x = -0.34$, $y = -0.60$, $z = -0.14$, $P < 0.01$ corrected). In Turner syndrome, the equivalent correlation was negative. Positive feedback from SCR enhances the cognitive appraisal of fearful faces in normal females, but this feedback loop appears not to be functioning normally in the Turner syndrome sample.

PPI analysis

At this stage in the analysis, we had a clear and consistent picture of the complementary roles played by the left and right amygdala in the recognition of fearful faces by normal females, which was consistent with our hypotheses. Selective activation of the right amygdala to fearful–neutral faces was associated with arousal, and this appeared to enhance cognitive appraisal. The left amygdala played the key role in this appraisal, through its connections with the left fusiform gyrus. In the X-monosomic females there was selective activation of both left and right amygdala to fearful faces, as in normal

females, but the pattern of activation over time was abnormal (Figs 2 and 3). Cognitive impairment in them seemed to be affected because of a lack of differential activation of the left fusiform gyrus. We hypothesised that, in Turner syndrome subjects, there is decreased fear-dependent functional connectivity between the left amygdala and the left fusiform gyrus. We formally tested this hypothesis with a PPI analysis (Friston *et al.*, 1997). A PPI analysis allows the delineation of areas of the brain that exhibit condition-specific covariation with a given reference ROI (i.e. the amygdala in the present analysis). Neural responses to fearful and neutral faces in left medial amygdala (maximal voxel: $x = -16$, $y = -8$, $z = -26$) were used as a covariate of interest to identify brain regions, where differential event-related responses to fearful faces exhibited a positive covariation with that left medial amygdala activity. In effect, we correlated the magnitude of amygdala response activity across the entire brain for the fear versus neutral contrast. We then tested for differences in this fear-dependent covariation between Turner syndrome with normal females.

There was a significant difference between groups in fear-dependent responses with left fusiform gyrus activity (maximal voxel $x = -44$, $y = -66$, $z = -12$; $P < 0.01$, corrected) covarying positively with left medial amygdala responses in normal females, but not in Turner syndrome (Fig. 4). This fear-specific decrease in fusiform-amygdala covariation as a function of group is consistent with our prediction that amygdala-fusiform connectivity is impaired in case females.

Discussion

This study provides evidence that the arousal and cognitive appraisal functions of the amygdala, in response to fearful faces, can be doubly dissociated. Previous reports of individuals with anteromedial temporal lesions have shown that cognitive performance can be intact, albeit diminished, in the absence of the right amygdala and its associated arousal responses (Glascher and Adolphs, 2003). Left amygdala activation has been more closely correlated with cognitive performance in some studies (Killgore and Yurgelun-Todd, 2001; Williams *et al.*, 2005*b*), although it cannot mediate normal responses in the absence of the right amygdala and may play a critical role in processing arousal in order to enhance cognitive performance, by decoding the arousal signalled by the threatening stimulus (Glascher and Adolphs, 2003). We have demonstrated that cognitive performance can be seriously impaired by a functional dissociation between the roles of the left and right amygdala, in a condition (X-monosomy) where both amygdala are structurally grossly normal although enlarged relative to normal females (Good *et al.*, 2003). We have also shown that they share a common pathway to cognitive appraisal of threat (signalled by a fearful face) in left fusiform gyrus. These findings support the hypothesis that the left and right amygdala play different but complementary roles in the appraisal of emotionally arousing

visual perceptions, and indicate new directions for research on how cortical and autonomic processes interact in the evaluation of negative facial stimuli.

Damasio (1995) proposed, in his 'somatic marker hypothesis', that humans normally use somatic internal responses to emotionally arousing stimuli to inform and guide cognitive appraisal. In this study, we show autonomic responses can be intact, in the absence of accurate cognitive appraisal. Turner syndrome females activate bilateral amygdala to fearful face stimuli, and this activation is correlated with an intact SCR (although the temporal pattern of arousal is not normal). Nevertheless, in a substantial proportion of cases their cognitive appraisal of facial expressions is equivalent to patients with a bilateral amygdalectomy. Our findings are in keeping with Glascher and Adolphs (2003) who proposed the right amygdala participates in rapid autonomic and automatic response to a visual emotional stimulus, but the left amygdala is engaged in cognitive appraisal of such stimuli through its interconnections with neocortical association centres (Amaral *et al.*, 1992). This process we suggest is impaired in our case females. [In view of the complexities of gender differences in amygdala activation, in response to emotionally arousing stimuli, we did not include males in this analysis; see McClure *et al.* (2004) for evidence that males and females show differential responsiveness of amygdala to fearful faces.]

Our first prediction, that amygdala activity in response to threat-related (fearful) faces presented in full awareness would be intact in X-monosomic females, was supported. The findings with regard to the right amygdala were consistent with the preliminary behavioural studies we had conducted, using a fear-conditioning paradigm. X-monosomic females were impaired on the explicit cognitive appraisal task, but contrary to our expectations their performance was not correlated with left amygdala activation. Left amygdala activation positively correlated with cognitive performance in normal females. Our second prediction, that right amygdala activation would be normal, and its association with arousal as measured by the SCR would be intact in Turner syndrome was also supported. The correlation between right amygdala responses and the SCR (fear–neutral faces) was similar in both samples.

Finally, we predicted cognitive performance in face emotion recognition skills would be correlated with activation in the fusiform cortex. Note, that the cognitive task was not performed in the scanner but on a separate and independent occasion. We found that a deficit in recognising fear in the X-monosomic sample was associated with a lack of correlation between activity in the left amygdala activation and the fusiform cortex (unlike normal comparisons). The explanation for this dissociation in the X-monosomic sample appears to lie in findings relevant to the third prediction, namely, that cognitive performance in both groups would be correlated with activation of fusiform gyrus. Contrary to expectations, activation of the left (but not the right) fusiform gyrus was crucially associated with explicit performance on the task in both groups but in X-monosomy the magnitude of response was diminished and it was not closely correlated with left
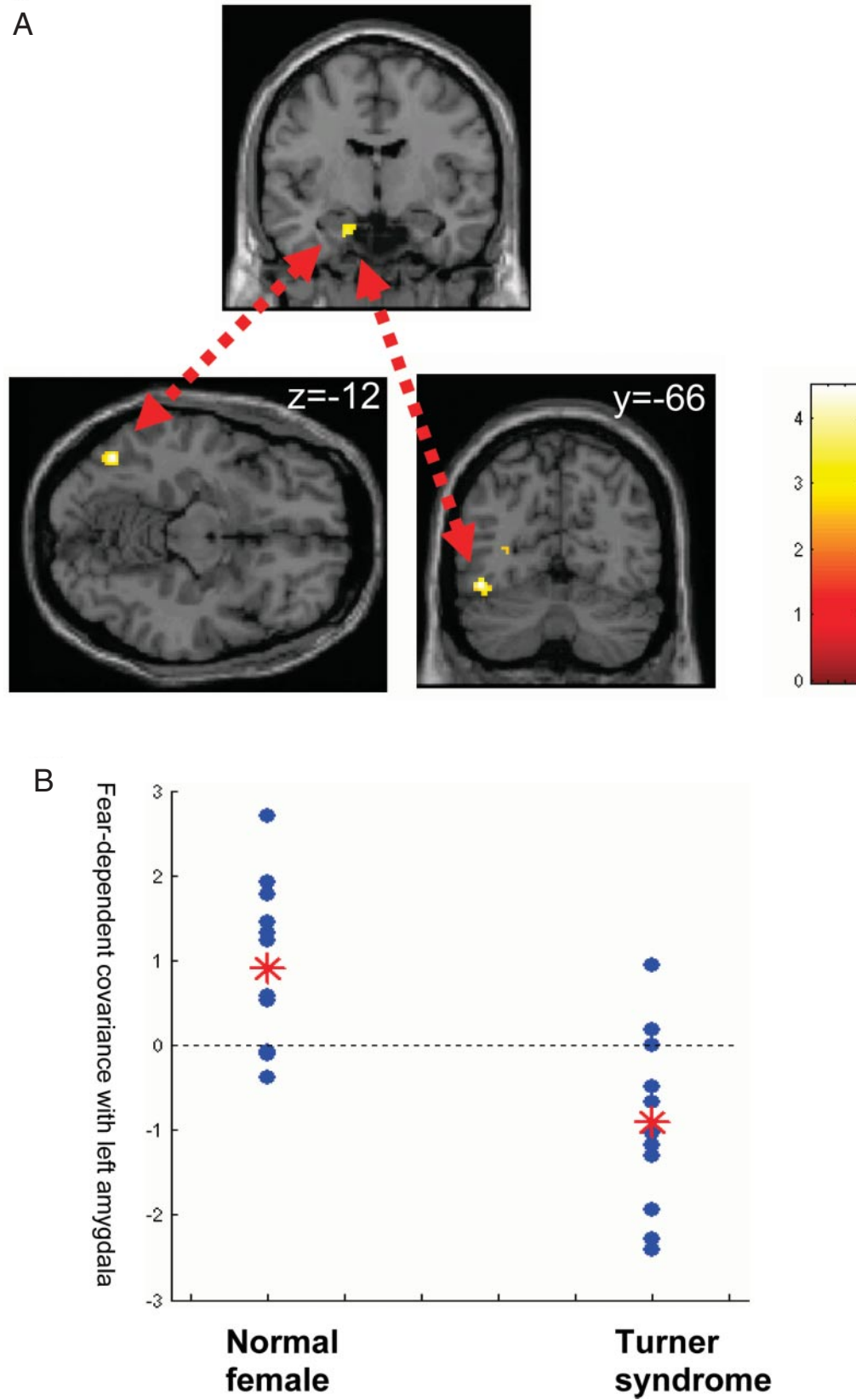
Fig. 4 (**A**) SPM figure displaying a region of left fusiform gyrus (maximal voxel: $x = -34$, $y = -60$, $z = -14$), where BOLD fMRI responses covaried positively differential left amygdala BOLD fMRI responses to fearful faces in 46,XX subjects but not in 45,X subjects. (**B**) Plot of covariation of BOLD fMRI responses to fearful faces in left fusiform gyrus and left medial amygdala in 45,X and 46,XX subjects. Mean covariation for each subject group is indicated with an asterix.

amygdala activation. In the comparison group greater SCR were correlated with better performance on the cognitive task, supporting the hypothesis that in normal individuals there is functional integration between autonomic responses and cognitive evaluation of a threatening stimulus. This contrasts with findings for our Turner syndrome subjects who showed no such positive correlation, despite elevated SCR, implying lack of functional integration. Taken together, these findings show that in the condition of X-monosomy there are several related deficits associated with the impaired cognitive response to the presentation of a fearful face (i.e. inability accurately to classify the emotion). First, there is an absence of a significant correlation between cognitive performance and activation of either amygdala. Second, activation of the left amygdala is functionally dissociated from that of the left fusiform activation. Third, autonomic arousal (reflecting right amygdala activation) is present, but is dissociated from left fusiform responsiveness.

The common association of left fusiform gyrus activation with fear recognition performance in both groups, and the difference between Turner syndrome and normal female subjects in covariation of SCR with left fusiform gyrus activation are intriguing observations. Neocortical sensory processing of emotionally salient stimuli may be enhanced via autonomic feedback connections (Williams *et al.*, 2004*a*). The strong correlation between fusiform responses to fearful faces with SCRs in normal female subjects could, therefore, reflect the emotional enhancement of sensory processing that contributes to enhanced performance on fear recognition. Conversely, the absence of fear-related SCR-fusiform co-variation in Turner syndrome females indicates disruption of this emotional enhancement of sensory responses, thereby contributing to the fear recognition deficit observed in these subjects. We conclude that in the Turner syndrome females, the feedback loop between autonomic processing in amygdala and responses in fusiform gyrus is abnormal. We can speculate that the reason for this is reflected in the unusual pattern of activation seen to fearful faces in that group (Fig. 3). Studies of amygdala responses to repeated exposure to fearful facial expressions (e.g. Phillips *et al.*, 2001) indicate that the right normally shows earlier, and more rapid, habituation than the left amygdala. It is possible that the functional disconnection between left amygdala and left fusiform gyrus reflects an abnormal pattern of habituation. A caveat here is the possibility that the two groups responded differently to the overt task (gender discrimination) in the scanner: ideally we would have had response times recorded to the button press, and would have conducted a passive emotional-face viewing task outside the scanner with SCR recordings, to rule out group differences in SCR to the forced-choice task.

The pattern and profile of deficit in the recognition of facial emotions by Turner syndrome females was similar in profile and in severity to that reported for individuals with bilateral amygdala lesions (Adolphs *et al.*, 1994; Calder *et al.*, 1996; Broks *et al.*, 1998). They were impaired in the recognition primarily of fear (Sato *et al.*, 2002; Hariri *et al.*, 2003), but also in their recognition of angry faces, which are also sensitive to amygdala lesions (Adams *et al.*, 2003). We noted previously (Lawrence *et al.*, 2003*a, b*) that Turner syndrome females have problems in the recognition of complex emotions, especially with linking complex emotional expressions to emotional labels. This deficit implicates the left amygdala in particular. We did not specifically obtain ratings of fearful face targets on an arousal dimension as was done by Adolphs *et al.* (2002), but we believe that had we done so these would have been impaired in case women compared to controls. We note that the subjective experience of fear in response to fearful visual stimuli is much reduced in Turner syndrome (Good *et al.*, 2003).

Deficits in cognitive appraisal of negative emotional faces in Turner syndrome would be, we predicted, causally linked to diminished reactivity of the left amygdala and the impaired functional connectivity between left amygdala and face processing cortex in the fusiform gyrus. We did not find group differences in the mean left amygdala response, although the temporal profile of activity was strikingly different in the two samples. We did, however, show impaired functional connectivity in the Turner syndrome group between the left amygdala and fusiform cortex. Fusiform cortex receives prominent feedback projections from the amygdala (Amaral *et al.*, 1992), which probably enhances processing of (negative) emotional stimuli (Morris *et al.*, 1998; Sugase *et al.*, 1999). The fusiform gyrus is activated more by fearful than neutral faces (Hadjikhani and de Gelder, 2003), and amygdala's influence on the fusiform could underlie the particular saliency of facial emotion stimuli (Lane *et al.*, 1999; Vuilleumier and Schwartz, 2001). Failure in connectivity may be associated with failure to provide appropriate verbal responses to recognition of emotions (Strange *et al.*, 2000; Anderson and Phelps, 2001).

In our data, activations of both the left and right amygdala were positively correlated with explicit performance, and to similar degrees, in normal females, but the final common pathway to determining accuracy in discriminating fearful faces seemed to be activation of left fusiform gyrus. Lateralization of amygdala activation could reflect verbal and non-verbal hemispheric asymmetries, typically ascribed to higher cortical functions in humans (Anderson *et al.*, 2000). Left lateralized amygdala responses have been previously reported to explicit (i.e. unmasked) presentations of fearful faces (Breiter *et al.*, 1996; Morris *et al.*, 1996; Phelps *et al.*, 2001; Thomas *et al.*, 2001; Wright *et al.*, 2001; Vuilleumier *et al.*, 2002). Others have found right amygdala activation predominates (Anderson *et al.*, 2000, Adolphs *et al.*, 2001). We agree with Glascher and Adolphs (2003) that these conflicting results may be explained by task-specific amygdala activation as proposed by Hariri *et al.* (2002), and the findings of this study strongly support that hypothesis. The pattern of dissociations we observe in our X-monosomic females adds a new dimension to the debate about the relationship between amygdala function, autonomic arousal, and the cognitive appraisal of negative facial cues. We show that functional connectivity between the left amygdala and left fusiform gyrus plays a critical role in such appraisal, and that the magnitude of

the extrastriate cortical response to a fearful face is directly correlated with cognitive performance in both normal and X-monosomic females.

Females with Turner syndrome usually show normal verbal abilities, but most have relatively poor visuospatial skills (Temple and Carney, 1995). The impairment in their visuospatial abilities is, however, not closely correlated with their lack of ability to perform social cognitive tasks, and does not explain their selective impairment in the appraisal of fearful faces (Lawrence *et al.*, 2003*a*, *b*). Although Turner syndrome is associated with ovarian dysgenesis (Ostberg and Conway, 2003) all Turner subjects in the current study were on oestrogen replacement therapy, and had so been since an average age of 15 years. However, an estrogenic effect on prepubertal brain development is a possibility. Impairments in visuospatial abilities have been found to persist into adulthood in X-monosomic females who had been treated with estrogen replacement therapy (Ross *et al.*, 2002). Recently, Everhart *et al.* (2004) evaluated face-processing skills in a heterogeneous sample of Turner syndrome females, of whom the majority were not taking estrogen-replacement therapy (at a mean age of 13.5 years). They conclude that the condition is associated with abnormal hemispheric organization and specialization for face recognition memory, and speculate this could be due to estrogenic deficiency during the prepubertal period.

In conclusion, we demonstrate specific deficits in the cognitive appraisal of threat can have functional origins, as well as being related to structural damage. These functional origins appear to be related to dosage-regulation problems in a certain class of X-linked genes that escape X-inactivation and are required in two copies for normal female neural development (Jacobs *et al.*, 1997; Disteche, 1999; Clement-Jones *et al.*, 2000; Boumil and Lee, 2001). There may be additional modifying effects of insufficient sex steroid exposure, but these are currently speculative. Accordingly, we provide the first evidence that the binding of somatic (bodily arousal) responses to cognitive appraisal of emotional stimuli (Damasio, 2000) has a genetic substrate. Our earlier research (Good *et al.*, 2003) indicates the genetic mechanism responsible is associated with one or more X-linked genes lying in a 5 Mb region on the X-chromosome at Xp11.3-4.

Acknowledgements

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