Social Cognitive and Affective Neuroscience Advance Access published January 27, 2014

doi:10.1093/scan/nst190 SCAN (2014) 1 of 8

A comparison of neural correlates underlying social cognition in Klinefelter syndrome and autism

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Klinefelter syndrome (KS) is a genetic syndrome characterized by the presence of an extra X chromosome that appears to increase the risk of psychopathology, such as autism symptoms. This study used functional magnetic resonance imaging to determine underlying mechanisms related to this risk, with the aim of gaining insight into neural mechanisms behind social-cognitive dysfunction in KS and autism, and understanding similarities and differences in social information processing deficits. Fourteen boys with KS, seventeen boys with autism spectrum disorders (ASD) and nineteen non-clinical male controls aged 10–18 years were scanned while matching and labeling facial expressions (i.e. face processing and affect labeling, respectively). No group differences in neural activation were found during face processing. However, during affect labeling, the ASD group showed increased activation in the amygdala compared with controls, while the KS group showed increased activation in frontal areas compared with both controls and the ASD group. No group differences in task performance were found. Although behavioral symptoms of social dysfunction appear similar both in boys with KS and ASD, this is the first study to demonstrate different underlying etiologies. These results may aid in identifying different pathways to autism symptoms, which may help understanding variability within the ASD spectrum.

Keywords: Klinefelter; autism; social cognition; fMRI; facial affect processing

INTRODUCTION

Klinefelter syndrome (KS) is characterized by the presence of an extra X chromosome in men, leading to an XXY karyotype. Prevalence estimates vary from 1:500 to 1:1000. In addition to physical consequences such as above average height, endocrinological imbalances and infertility, the presence of an extra X chromosome may also affect (neuro)psychological development (Sorensen 1992; Herlihy *et al.* 2011). The X chromosome contains many genes that affect brain development, which may result in cognitive and behavioral impairment, although hormones may also influence the expression of KS symptoms (Verri *et al.* 2010; Bruining *et al.* 2011). While intellectual functioning appears to be at the lower end of the normal range, language disorders and reading disabilities are often reported (Boada *et al.* 2009). Additionally, a range of executive functioning deficits has been reported (Boada *et al.* 2009; Van Rijn *et al.* 2009; Lee *et al.* 2011). Clearly, KS affects several areas of cognitive functioning.

Moreover, KS appears to increase the risk of psychopathology. It is important to understand the underlying cognitive and neural mechanisms driving this risk. For instance, several studies have proposed an association between KS and autism symptoms such as social anxiety, social withdrawal, reduces assertiveness, impaired emotion regulation, and communicative difficulties. Studies show that 5–25% of individuals with KS are diagnosed with autism spectrum disorder (ASD) (Geschwind and Dykens 2004; van Rijn *et al.* 2008b; Bruining *et al.* 2009; Tartaglia *et al.* 2010; Bishop *et al.* 2011; Cordeiro *et al.* 2012; van Rijn *et al.* in press). It is important to determine what underlying mechanisms cause the heightened risk for ASD in boys with KS. As these boys represent a genetically homogeneous high risk group for ASD, this will not only further insight into mechanisms behind social problems in children with genetic abnormalities, but findings may also have implications for understanding variability within the ASD phenotype.

In order to understand the risk mechanisms driving vulnerability for ASD, it may be important to focus on social cognition and its neural correlates. For example, the processing of affective information from faces, one of the most crucial sources of social information, appears to be affected in individuals with ASD. In individuals with KS, impairments in facial affect processing have also been found (van Rijn *et al.* 2006). For example, adult males with KS appear to have difficulties interpreting social-emotional cues from faces, such as labeling facial expressions and detecting gaze direction (van Rijn *et al.* 2006). Although both disorders are associated with impairments in social cognition, it is important to assess whether this is a different type of deficit because facial affect processing involves a number of information processing steps. For example, there may be specific deficits in face processing, the recognition and processing of faces, or deficits in higher order cognitive processes such as affect labeling, the identification and labeling of emotions. These different types of deficits may become evident in neural activation patterns during facial affect processing. Magnetic resonance imaging and especially functional magnetic resonance imaging (fMRI) studies may thus be useful in addition to neurocognitive and clinical research methods, as these may provide detailed insight into the processing of social information on the level of neural activation patterns. However, studies focusing on neural mechanisms mediating social problems in boys with KS are lacking.

Anatomical studies thus far indicate that individuals with KS have smaller total cerebral, frontal, temporal and caudate volumes, and the cortex in temporal and frontal regions is thinner (Giedd *et al.* 2007). Merely a handful of fMRI studies have been performed, only one of which in children, which focused on language processing (Steinman *et al.* 2009). fMRI studies focusing on neural networks subserving

Received 18 July 2013; Accepted 30 December 2013

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social functioning in children with KS, and studies comparing brain activation patterns in boys with KS and boys with ASD are currently non-existent. This study will therefore compare boys with KS, ASD, and non-clinical controls between the ages of 10 and 18 using two fMRI tasks: one focusing on face processing and the other focusing on affect labeling. Differences in brain activation patterns between these groups may help differentiate between different types of social dysfunction.

MATERIALS AND METHODS

Participants

Fourteen boys with KS [$M_{age} = 14.02$ (SD = 2.59)], seventeen boys with ASD [$M_{age} = 12.41$ (SD = 1.94)] and nineteen non-clinical male controls [$M_{age} = 12.03$ (SD = 2.36)] were included in analyses. Analysis of variance revealed a significant effect of group on age [$F(2,48) = 3.310$, $P = 0.045$], for which *post hoc* testing showed this was due to a borderline significant difference in age between the KS group and controls ($P = 0.051$), with the KS group having a higher mean age.

The KS group was recruited using different strategies, to avoid recruitment bias as much as possible. The sample consisted of children who were actively followed up after prenatal diagnosis with the help of clinical genetics departments in the Netherlands and Belgium, as well as children whose parents actively sought information about the condition of their child (recruited through support groups and calls for participants, with the help of the Dutch Klinefelter Association), and those who were seeking help for developmental problems (recruited through pediatricians, psychologists, psychiatrists and clinical genetics departments). The ASD group was recruited through the Center for Autism, a pediatric psychiatric outpatient department in the Netherlands. All boys with ASD were classified according to the DSM-IV criteria (American Psychiatric Association 1994), using the Autism Diagnostic Interview-Revised (ADI-R) (Lord *et al.* 1994), parental questionnaires, parental interviews, developmental history and family history, information from primary physicians as well as elaborate expert clinical observations. All ASD diagnoses were reached through consensus among a multidisciplinary team of mental health professionals, including board-certified pediatric psychiatrists with experience in the field of autism. Non-clinical controls were recruited through schools in the western part of the Netherlands and screened for psychopathology. None scored in the clinical range (>70) on the Child Behaviour Checklist (CBCL) (Achenbach 1991).

Inclusion criteria for all participants were Dutch as primary language and an age between 10 and 18 years. Exclusion criteria were a recent history of substance abuse, intellectual disability (<60 IQ points), scan or motion artifacts (i.e. mean displacement >5 mm) as well as neurological conditions (e.g. structural brain damage due to prenatal/birth complications, tumors, strokes or diseases affecting the central nervous system). All participants and their parents received a complete description of the study and provided written informed consent prior to participation, in accordance with the Declaration of Helsinki. All children received a gift card for participation, and travel costs were reimbursed. The experiment was approved by the Ethical Committee of the Leiden University Medical Center, Leiden, The Netherlands.

Procedure

All scans were administered in one morning or afternoon at the Leiden University Medical Center (Leiden, The Netherlands). Upon arrival, participants were screened for metals or other dangerous physical conditions using the MRI safety check list. Subsequently, they were escorted to the mock scanner, which was used to acclimate participants to the scanner environment. A laptop computer was used for task instruction. Participants were allowed to practice as much as needed to fully grasp task requirements. Prior to fMRI scanning, participants underwent anatomical scanning while watching a movie.

Outcome measures

Intellectual functioning

Participants completed the Block Design and Vocabulary subtests of the Dutch adaptations of the Wechsler Scales (WAIS-III and WISC-IV) (Wechsler 1997; Wechsler 2005). The subtest Vocabulary measures the degree to which one has learned, is able to comprehend, and verbally expresses vocabulary. The subtest Block Design measures spatial perception, visual abstract processing, and problem solving. These two subtests form the V-BD short form. The V-BD short form is often used to estimate full-scale IQ (FSIQ) according to the algorithm [2.9*(sum of normed scores)+42] (Campbell 1998). The V-BD short form correlates highly with WISC FSIQ ($r = 0.88$) (HerreraGraf *et al.* 1996) and has been found valid for the estimation of intelligence, with good reliability ($r = 0.91$) and validity ($r = 0.82$) (Campbell 1998).

Autism spectrum symptoms

The Social Responsiveness Scale (SRS) (Constantino and Gruber 2005) is a 65-item parent-report questionnaire that was used to assess the degree of autism spectrum symptoms. It includes items that ascertain social awareness, social cognition, social communication, social motivation, and autistic mannerisms. Higher scores indicate stronger autism traits. A validation study (Constantino *et al.* 2003) indicated that the SRS was highly correlated with the Autism Diagnostic Interview-Revised (ADI-R) (Lord *et al.* 1994). Coefficients were higher than 0.64 between SRS scores and all ADI-R scores. Total SRS scores were used as an indication of autism spectrum symptoms.

Social cognition fMRI task

The 'matching/labeling' fMRI task was used to assess participants' neural activation during face processing (the matching of facial expressions) and affect labeling (the labeling of facial expressions). The task consisted of 64 trials in which stimuli were to be labeled and 64 in which stimuli were to be matched. In each task, half of the stimuli (i.e. 32) consisted of faces and half consisted of objects. This resulted in four conditions. In the face matching condition, participants were instructed to select the face that best matched the facial expression of faces at the top of the screen, from two faces at the bottom corners of the screen. In the face labeling condition, participants were instructed to select one of two semantic labels presented at the bottom corners of the screen. In the object matching condition, participants were asked to match pictures of either bags or coats at the top of the screen, with pictures of bags and coats at the bottom corners of the screen. In the object labeling condition, participants were asked to assign a semantic label ('bag' or 'coat') to pictures of bags or coats at the top of the screen. Stimuli used in the object trials were selected from the colored version of the validated Snodgrass and Vanderwart picture set (Snodgrass and Vanderwart 1980; Rossion and Pourtois 2004). Stimuli used in the face trials were selected from the Karolinska Directed Emotional Faces (KDEF) (Lundqvist *et al.* 1998). Examples of trials from each condition are shown in Figure 1. The object matching and face matching conditions were contrasted in analysis to provide an indication of 'face processing' activation, while the face matching and face labeling conditions were contrasted to provide an indication of 'affect labeling' activation.

This task was specifically aimed at activating social networks, instead of challenging participants' cognitive abilities. Consequently, task

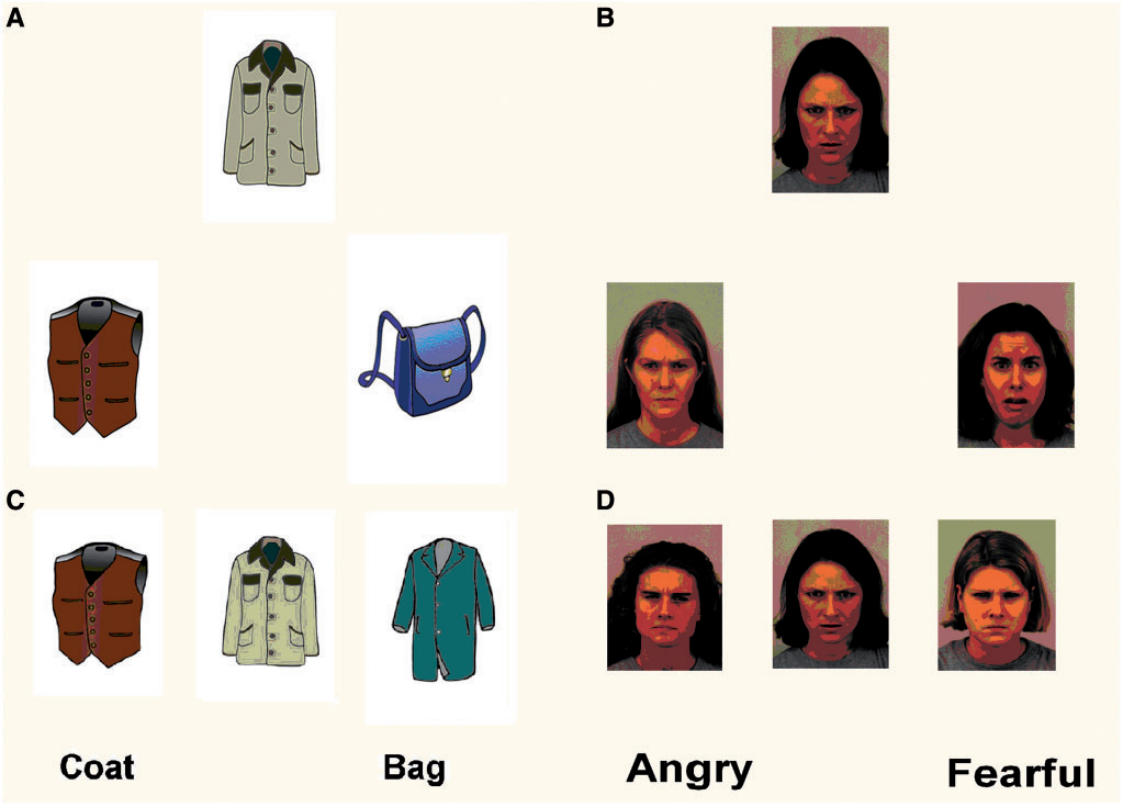

Fig. 1 Examples of trials from all four conditions of the matching/labeling task. (A) Object matching; (B) Face matching; (C) Object labeling; (D) Face labeling.

demands were relatively low and did not mirror real-life social situations, in which responses are immediate and non-dichotomous. This was done to ensure activation of social networks without involving cognitive functions related to task complexity. Prior to starting the task, an introduction was presented on the screen (lasting 128 s), in which task instructions were repeated. The task consisted of 16 counter balanced blocks of eight trials (four blocks in each condition) and was divided into two halves, with a short break in between. Each stimulus remained on the screen for 5 s with a 600 ms intertrial interval. Answers were provided by pushing buttons with the left and right index fingers. Task performance was saved in Eprime data files.

fMRI data acquisition

Scanning was performed on a 3-Tesla Philips Achieva whole body MRI scanner (Philips Healthcare, Best, The Netherlands), using an 8-channel SENSE receiver head coil. For the fMRI task scans, a total of 326 dynamic scans (two times 163 volumes) were acquired, including two dummy scans preceding both scans to allow for equilibration of T1 saturation effects [time repetition (TR) = 2.2 s, time echo (TE) = 30 ms, flip angle = 80°, 38 transverse slices, FOV = 220 × 220, 2.75 mm isotropic voxels, 0.25 mm slice gap]. Visual stimuli were projected onto a screen that was viewed through a mirror mounted onto the head coil. For registration purposes, T1-weighted anatomical and high-resolution EPI scans were obtained prior to functional scans [T1-weighted scans: TR = 9.75 ms, TE = 4.60 ms, flip angle = 8°, 140 transverse slices, 1.167 mm × 1.167 mm × 1.200 mm, FOV = 224.000 × 177.333; high resolution EPI scan: TR = 2.2 ms, TE = 30 ms, flip angle = 80°, 84 transverse slices, FOV = 220 × 220, in-plane resolution = 1.964 mm × 1.964 mm, slice thickness = 2 mm]. All anatomical scans were reviewed and cleared by a radiologist. No anomalous findings were reported.

fMRI data analysis

Preprocessing. fMRI data analysis was performed using FMRIB's Software Library's (FSL) FMRI Expert Analysis Tool (FEAT) version 4.1.6 (Smith *et al.* 2004; Woolrich *et al.* 2009; Jenkinson *et al.* 2012). The following settings were applied during first-level analysis: MCFLIRT motion correction (Jenkinson *et al.* 2002); BET brain extraction (Smith 2002); spatial smoothing using a Gaussian kernel of FWHM 8.0 mm; 190 s high-pass temporal filtering and FILM prewhitening (Woolrich *et al.* 2001). In order to compare activity at the group level, fMRI data were registered to the high-resolution EPI image, the high-resolution EPI image to the T1-image and the T1-image to the 2 mm MNI standard space template (Jenkinson and Smith 2001; Jenkinson *et al.* 2002). The resulting registration matrices were combined to describe the fMRI to MNI space transformation.

First-level analysis. Two designs were created. One design excluded object matching as a regressor (using it as an implicit baseline) and one excluded face matching as a regressor. This was done for both task halves separately. Two contrasts were set up to compare neural activation patterns. In the 'face matching > object matching' [1 0] contrast, significant results indicated more brain activation during face matching than object matching and were used as an indication of face processing activation. In the 'face labeling > face matching' [1 0] contrast, significant results indicated more brain activation during face labeling than face matching and were used as an indication of affect labeling activation. All three groups were mutually compared on both contrasts.

Higher level analysis. First, task halves were combined to create one lower level statistical map per participant for each of the lower level contrasts, using a fixed effects analysis. At the group level, a mixed

effects analysis was employed (FLAME 1) (Smith *et al.* 2004). Correction for multiple comparisons across all brain voxels was done using cluster-based thresholding, using an initial cluster-forming threshold of $Z > 2.3$ and a corrected $P < 0.05$. Activation clusters were labeled using the Harvard-Oxford cortical and subcortical structural atlases (Frazier *et al.* 2005; Desikan *et al.* 2006; Makris *et al.* 2006; Goldstein *et al.* 2007), as well as the Jülich histological (cyto- and myeloarchitectonic) atlas (Amunts *et al.* 1999; Amunts *et al.* 2000; Eickhoff *et al.* 2005; Eickhoff *et al.* 2006; Eickhoff *et al.* 2007). Labels with reported percentages of ≥10 were deemed relevant.

RESULTS

Intellectual functioning

For one boy with KS, IQ data were missing. All IQ scores are presented in Table 1. A significant main effect of group on overall IQ was found [$F(2,46) = 10.4$, $P < 0.001$], due to a significant difference in IQ scores between the KS group and both the control and ASD groups, with the KS group having lower mean IQs than controls ($P < 0.001$) and the ASD group ($P = 0.003$). In a second analysis, scores on the two separate IQ subtests, Block Design and Vocabulary, were compared across groups. Multivariate analysis showed a significant main multivariate effect of group [$F(4,92) = 45.0$, $P < 0.001$]. The univariate results showed no significant main effect of group on Block Design ($P = 0.13$). There was, however, a significant main effect of group on Vocabulary [$F(2,46) = 12.5$, $P < 0.001$], which was solely driven by lower scores in the KS group as compared with the control group ($P < 0.001$) and the ASD group ($P = 0.001$). To prevent group differences in aspects of IQ from confounding fMRI task performance results, Block Design and Vocabulary scores were used as covariates in analysis of task performance.

Table 1 Mean overall IQ scores and mean normscores for IQ subtests, including standard errors

	Overall IQ	Block Design	Vocabulary
Controls ($n = 19$)	103.9 ± 3.5	10.3 ± 0.71	11.0 ± 0.83
KS ($n = 13$)	79.0 ± 4.2	8.1 ± 0.85	4.5 ± 1.0
ASD ($n = 17$)	96.5 ± 3.7	9.7 ± 0.75	9.0 ± 0.88

Table 2 Activation clusters for 'face processing' (face matching > object matching)

No. of voxels	Corrected *P*	Z_{max} value	*x*, *y*, *z*	Structures
Mean activation controls				
2240	<0.001	4.42	40, 4, 32	Right precentral gyrus, middle frontal gyrus, inferior frontal gyrus/ pars opercularis (Broca)
2089	<0.001	4.17	22, −2, −17	Right amygdala
1860	<0.001	5.17	42, −48, −24	Right temporal occipital fusiform cortex
Activation KS deviant from controls Non-significant				
Activation KS deviant from ASD Non-significant				
Activation ASD deviant from controls Non-significant				

Autism symptoms

SRS scores were available for 19 boys in the control group [$M_{srs} = 29.8$ (SD = 22.9)], 10 in the KS group [$M_{srs} = 75.7$ (SD = 26.4)] and 14 in the ASD group [$M_{srs} = 96.5$ (SD = 37.6)]. A significant effect of group on SRS scores was found [$F(2,40) = 22.37$, $P < 0.001$], with mean scores in both the KS ($P = .001$) and ASD ($P < 0.001$) groups being significantly higher than in controls. No significant difference in mean scores between the KS and ASD groups was found.

fMRI activation patterns

'Face processing': face matching vs *object matching*

Controls. Mean activation results for controls are summarized in table 2. Significant activation in three clusters was found, i.e. right-sided frontal regions (Figure 2A), the amygdala (Figure 2B) and fusiform cortex (Figure 2C).

Clinical groups. No significant between-group differences in brain activation were found, i.e. the ASD and KS groups did not show activation that was deviant from controls.

'Affect labeling': face labeling vs *face matching*

Controls. Mean activation results for controls are summarized in Table 3. Significant activation in two clusters was found, i.e. occipital regions (Figure 3A) and the left temporal pole (Figure 3B).

Clinical groups. The ASD and KS groups showed significantly different activation patterns as compared with controls. Activation results

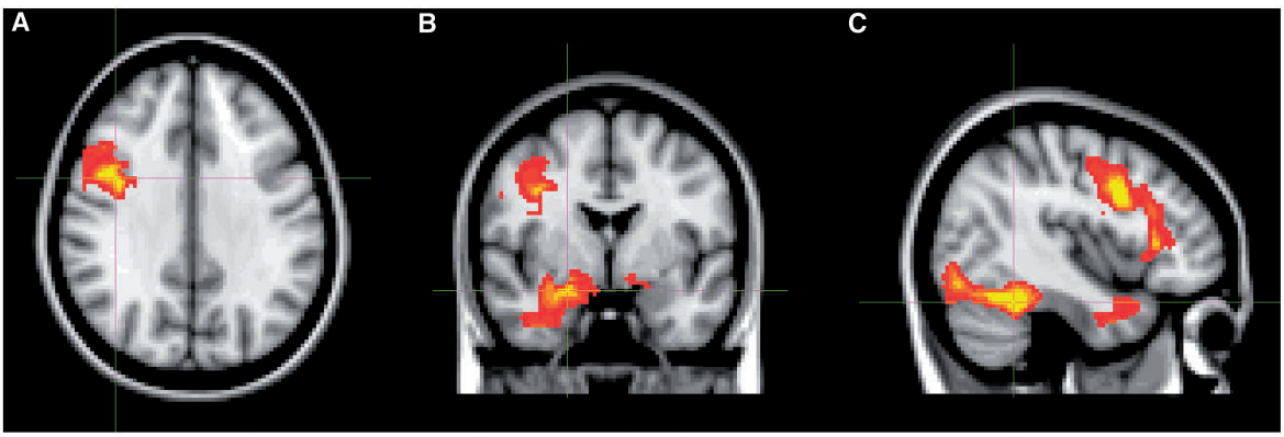

Fig. 2 Mean activation clusters in controls for 'face processing' (face matching > object matching). (A) Frontal activation; (B) Amygdala activation; (C) Temporal activation.

Table 3 Activation clusters for 'affect labeling' (face labeling > face matching)

No. of voxels	Corrected *P*	Z_{max} value	*x*, *y*, *z*	Structures
Mean activation controls				
5633	<.001	4.89	4, −88, 4	Intracalcarine cortex, occipital pole (V1), supracalcarine cortex, lingual gyrus
2109	<.001	4.36	−50, 14, −20	Left temporal pole
Activation KS more than controls				
1009	0.008	3.77	48, 16, 36	Right middle frontal gyrus (Broca)
Activation KS more than ASD				
1684	0.00024	4.57	48, 16, 36	Right middle frontal gyrus (Broca)
Activation ASD more than controls				
929	0.012	3.66	16, 0, −22	Right amygdala, parahippocampal gyrus (anterior)

for the KS and ASD groups are summarized in Table 3. Higher level analysis comparing the face labeling > face matching contrast across all groups resulted in one significant cluster of deviating neural activation in each group. Asking participants to label rather than match faces resulted in significantly more activation in the right middle frontal gyrus (including Broca's area) (Figure 3C) in the KS group than in both controls and the ASD group. In contrast, the ASD group showed more right amygdala activation (Figure 3D) than controls. To illustrate these significant group effects, uncorrected *Z*-values for all groups on the coordinates showing significant group differences are depicted in Figure 4 for both activation clusters.

Task performance

Task performance is summarized in table 4. Three controls were removed from analysis due to *Z*-scores >2.5, as it could not be excluded that these participants used the response box incorrectly. MANCOVA, covarying for Block Design and Vocabulary, showed no significant main multivariate effects of group ($P = 0.33$), Block design ($P = 0.34$) or Vocabulary ($P = 0.07$) on task performance. Accordingly, none of the univariate effects of group, Block Design, or Vocabulary, were significant.

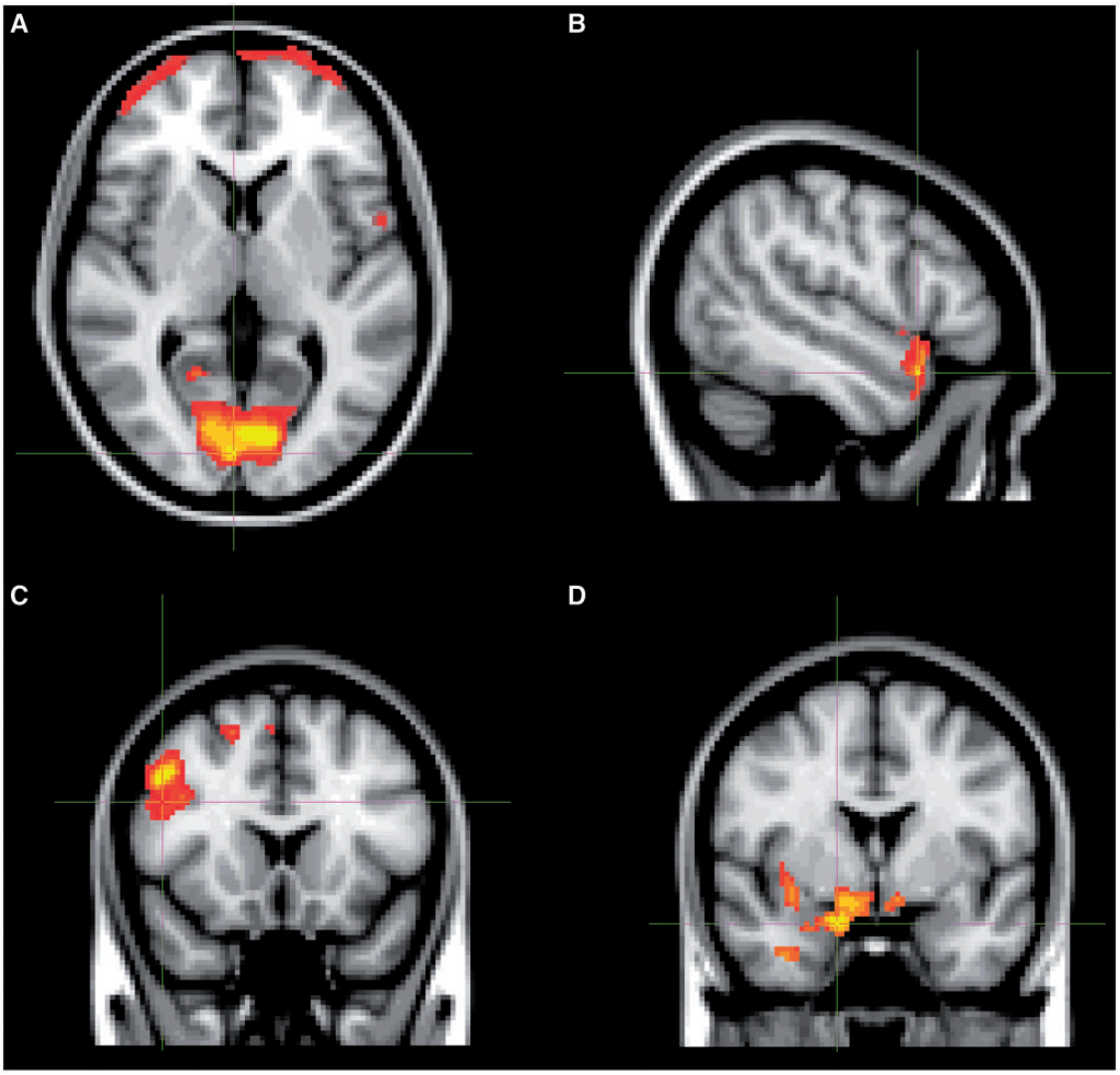

Fig. 3 Activation clusters for 'affect labeling' (face labeling > face matching). (A) Occipital activation controls; (B) Temporal activation controls; (C) Frontal activation KS group more than controls and ASD; (D) Amygdala activation ASD group more than controls.

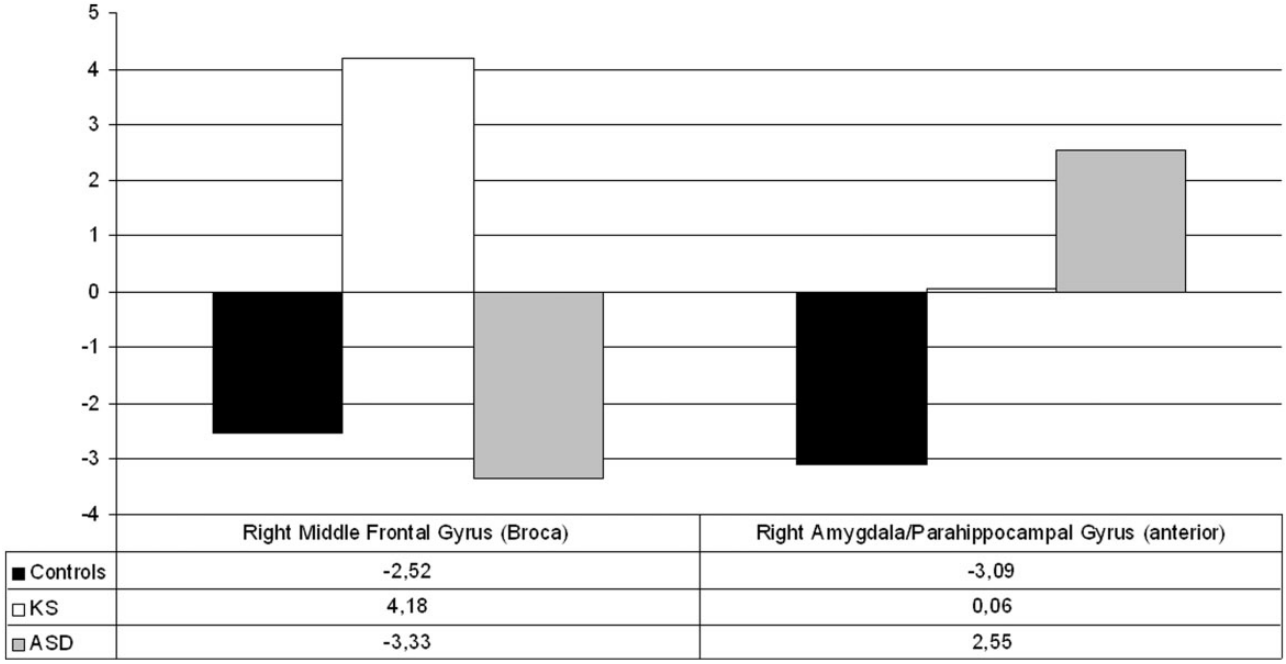

Fig. 4 *Z*-values in significant activation clusters for 'affect labeling' (face labeling > face matching).

Table 4 Estimated marginal means (corrected for covariates) for performance on the fMRI task

	Object matching	Face matching	Face labeling
Controls ($n = 16$)	30.4 ± 1.2	28.9 ± 1.4	29.3 ± 1.4
KS ($n = 13$)	26.5 ± 1.4	24.1 ± 1.6	24.8 ± 1.6
ASD ($n = 17$)	27.7 ± 1.1	24.9 ± 1.3	25.0 ± 1.3

Scores indicate mean number of correct answers and standard errors.

DISCUSSION

This fMRI study compared brain activation patterns in boys with an extra X-chromosome (XXY karyotype, KS), ASD and non-clinical controls during a social-cognitive (facial affect) processing task. During face processing, in which participants were instructed to match visually presented faces based on expressions, increased activation in right-sided frontal regions, the amygdala and fusiform gyrus was found in controls. These results suggest that these areas show increased activation specifically during face processing. The amygdala and fusiform cortex have been implicated in face processing in multiple studies (Morris *et al.* 1998; Critchley *et al.* 2000; Pizzagalli *et al.* 2002; Adolphs and Spezio 2006). No significant differences in brain activation were found between controls and the KS and ASD groups. This suggests that, compared with controls, face processing is not accompanied by more or less brain activation in these clinical groups than processing socially neutral information.

However, interesting group differences were found during affect labeling, i.e. the higher order processing of facial information. In controls, affect labeling was associated with significantly increased activation in occipital regions (V1) and the left temporal pole. Increased activation in the occipital cortex may be explained by the theory that processing socially relevant information may boost activation in a neural system involving the primary visual cortex (Lang *et al.* 1998). Moreover, the temporal pole is implicated in social semantic processing, which requires knowledge regarding social concepts (Ross and Olson 2010). Facial affect labeling requires such knowledge. Additionally, linguistic studies have implicated the left temporal pole in proper names processing, referring to naming specific entities instead of general classes of entities (in the current study, 'angry' or 'sad' as opposed to 'emotional') (Semenza 2011). This suggests a degree of higher order processing in controls during affect labeling, which is not present during face processing. Assigning a semantic label to a facial expression may be more demanding than matching facial expressions, as the latter could conceivably be accomplished by merely visually locating differences in perceptual features, as opposed to actually understanding the significance of facial expressions.

It was affect labeling that led to deviant activation patterns in the clinical groups. The ASD group showed significantly more activation in the right amygdala than controls. In contrast, the KS group showed more activation in the right middle frontal gyrus (including Broca's area) than controls. Crucial to the aim of the current study, this significant group effect also extended to the KS-ASD contrast, dissociating the KS group from the ASD group based on frontal activation. These results suggest more involvement of specific brain regions in the ASD and KS groups than controls during affect labeling. However, this concerned involvement of very different parts of the brain: the amygdala in the ASD group and frontal areas in the KS group. Possibly, boys with KS solve social issues through increased involvement of frontal functions, relying heavily on reasoning abilities, while boys with ASD seem to rely more on basic social networks involving the limbic system.

Taken together, the following conclusions can be drawn regarding neural activation in the ASD group. During face-specific processing, controls showed significant amygdala activation, suggesting the meaning of facial expressions is processed relatively automatically in non-clinical individuals. However, no significant differences in neural activation between controls and the ASD group were found, meaning boys with ASD do not show more or less amygdala activation. However, during affect labeling, the ASD group did show increased amygdala

activation compared with controls. This boost in amygdala activation may be explained by the hypothesis that during face processing, they apply a more perceptual feature-based approach ('spotting the differences') which is impossible during affect labeling. The latter requires social information processing, leading to an increase in amygdala activation.

For the KS group, results are different from the ASD group and lead to the conclusion that affect labeling is associated with deviant neural activation in more frontal areas of the brain. The current finding of increased activation in the middle frontal gyrus may signify compensatory mechanisms involving a higher order reasoning approach to social information processing. As this frontal structure also includes Broca's area, language functions may play a role in these mechanisms. Possibly, boys with KS do not label incoming social information intuitively, but rather attempt to use a 'reasoning' or more rational approach. These findings are in line with a study in adults with KS, in which increased activation in language-related areas in the right hemisphere was found during a language processing task (van Rijn *et al.* 2008a). However, others have found that boys with KS showed significantly reduced brain activation in areas associated with language and reading during a language-related task (Steinman *et al.* 2009).

It would be interesting to further assess the role of language skills in social-cognitive processing in individuals with KS. As is typically found, the KS group had lower IQ scores than the other groups, specifically on Vocabulary, which measures the degree to which one has learned, is able to comprehend, and verbally expresses vocabulary. This is important, as one would expect language skills to play a role in affect labeling. However, despite lower Vocabulary scores, there were no group differences in task performance during affect labeling when controlling for Vocabulary performance. Also, Vocabulary performance did not significantly contribute to task performance in the scanner. This implies that despite the verbal nature of the fMRI task, all groups were equally skilled in performing the scanner task. However, the finding of increased activation in Broca's area does imply compensatory mechanisms in the language domain during affect labeling. This supports a link between language and social cognitive processing in boys with KS, which should be studied more thoroughly in future studies in which more complex affect labeling skills are assessed.

Regarding limbic and temporal lobe networks associated with social information processing, decreased activation in the amygdala, fusiform gyrus, superior temporal sulcus and insula was found in adults with KS during a task focusing on judging face trustworthiness (van Rijn *et al.* 2012). It would be interesting to assess whether such a complex social-cognitive task also involves more frontal activation, as frontal activation may inhibit limbic activity (Berkman *et al.* 2009). Taken together, these studies point toward abnormalities in the fronto-amygdala emotion regulation circuitry.

A limitation of the current study was that the KS group had a significantly lower mean IQ and higher mean age. However, separate aspects of IQ (both spatial and verbal) were used as covariates in analyzing task performance. Additionally, task demands were intentionally kept to a minimum to ensure activation of social neural networks in all groups irrespective of intellectual level. Significant age differences may be of influence on the results, especially in children. However, from a developmental perspective, this could only result in an advantage for the KS group. Another limitation was the relatively small sample size, especially in the KS group, which may have led to lack of power in analyzing task performance and prevented correlational analysis between fMRI and cognitive data. In future studies, it would be interesting to assess connectivity networks during information processing to determine how brain areas work together in individuals with KS. Significant differences in these connectivity networks would corroborate the hypothesis of a specific ASD phenotype in these individuals. Additionally, it would be interesting to assess whether subtypes can be identified within the autism spectrum, e.g. those with more frontal deficits *vs* those with more limbic deficits.

The frontal abnormalities found in this study may underlie the reported social-cognitive deficits and social-behavioral problems. What the present study may contribute is increased understanding of specific underlying etiologies of impairments in terms of neural mechanisms. Conceivably, boys with KS who have high levels of autism symptoms or an ASD diagnosis may represent a subgroup with a specific etiology underlying social dysfunction. Although the behavioral parameters (i.e. SRS scores) indicate similar types of social dysfunction on a behavioral level, neuroimaging revealed different underlying etiologies. Studying individuals with genetic syndromes such as KS may aid in understanding and explaining variation within the broad ASD phenotype. It is important to identify specific subpopulations within the spectrum, as this contributes to tailored diagnosis and treatment (van Rijn *et al.* 2013). Using neuroimaging in addition to cognitive and behavioral measures may benefit this process.

FUNDING

This work was supported by the Netherlands Organization for Scientific Research (NWO) (016.095.060 to S.v.R).

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