

Impaired Activation of Face Processing Networks Revealed by Functional Magnetic Resonance Imaging in 22q11.2 Deletion Syndrome

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Background: 22q11.2 deletion syndrome (22q11DS) is a neurogenetic syndrome associated with a high rate of psychiatric disorders. Previous research has revealed distinctive cognitive deficits, including impaired face processing. However, the neuro-functional substrates underlying these deficits have not been explored. Our aim was to investigate facial and emotional processing in 22q11DS.

Methods: During event-related functional magnetic resonance imaging, 15 individuals with 22q11DS were compared with age- and gender-matched healthy control subjects on a simple visual categorization task (faces or houses). Each stimulus was presented twice, and faces had either neutral or emotional (fearful) expressions.

Results: Abnormal responses to faces were observed in 22q11DS, including a lack of normal face-selectivity in fusiform gyrus. By contrast, responses to houses were comparable across groups, with preserved selectivity in parahippocampal gyrus. Results also revealed a repetition-suppression effect for fearful faces in the right amygdala, which arose in healthy control subjects only, suggesting a lack of amygdala modulation by fear expression in 22q11DS.

Conclusions: Our results demonstrate selective anomalies in several brain regions critically implicated in visual and social function in 22q11DS. These findings suggest important new avenues for studying emotional processing and social deficits frequently observed in psychotic patients and establishing their relation to specific phenotypic manifestations in 22q11DS.

Key Words: Amygdala, deletion 22q11, face perception, functional MRI, schizophrenia, velocardiofacial syndrome

22q11.2 deletion syndrome (22q11DS) is a neurogenetic disorder associated with social (1–3), cognitive (4–6), and neuroanatomical (7–9) anomalies. Previous studies have suggested that these impairments might underlie the high incidence of psychosis in the syndrome, which is considered as a genetic model for schizophrenia (2,10). Psychosis might arise early on, with a high incidence of positive symptoms already apparent in affected children and adolescents (1,3). A longitudinal report demonstrated that 30% of affected individuals eventually develop psychosis (10). Both children and adults with 22q11DS also demonstrate other comorbid psychological problems, such as high levels of anxiety and phobia, attention-deficit/hyperactivity disorder (ADHD), and social withdrawal (2,11–13).

Recent studies have found marked impairments in face processing in 22q11DS, including face memory (14,15) and face discrimination (16). A perceptual origin for these deficits is suggested by difficulties in face identity matching (17) and in both featural and configural face processing (18). Such deficits suggest an inability to acquire normal expertise on face processing, possibly related to abnormal development of temporal lobe

circuits involved in visual recognition and social cognition. In keeping with this, anatomical studies have reported early decreases in fronto-temporal white matter (19) and posterior gray-matter volume (8,9), associated with enlarged posterior ventricles and displaced corpus callosum (4,20). These changes might disrupt early perceptual input and subsequent neuronal pruning within cortical networks of the temporal lobe that mediate visual recognition and social cognition. Accordingly, quantitative measures of temporal regions show relatively preserved volumes in young children with 22q11DS but greater reductions in adults (7,21,22), which could impact the specificity and organization of face and object processing throughout development in affected individuals.

However, despite numerous descriptions of the frequent social and psychological problems in 22q11DS, the neural underpinnings of such impairments in this syndrome remain unknown. Here we used functional magnetic resonance imaging (fMRI) to identify possible disturbances in the neural systems mediating face recognition and emotional processing in individuals affected by 22q11DS.

In the present study, we collected event-related fMRI data during a simple visual categorization task (faces and houses). Faces were shown with either neutral or emotional (fearful) expressions. This task allowed us to probe three major aspects of facial processing. First, we compared neural responses to pictures of faces and houses to determine the patterns of category-selective activations in visual cortex. Processing faces and their expressions is an essential social skill in humans and relies on a set of highly specialized brain regions, including visual cortices, associative cortices, and limbic areas such as the amygdala (23–25). Neuroimaging studies in normal subjects have established that face perception recruits selective regions in extrastriate visual cortex, especially lateral fusiform gyrus (FG) (26,27), whereas perception of houses and places activates a distinct region in parahippocampal gyrus (28). Thus, we could test

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whether deficits in 22q11DS are associated with selective anomalies in fusiform function specifically or rather with more diffuse deficits in cortical specialization. Second, by comparing neutral and fearful faces, we could determine any disturbances in brain areas normally activated by emotional expressions (i.e., superior temporal sulcus [STS], amygdala, and ventro-medial prefrontal areas) (23–25). Finally, as a third dimension of our paradigm, each individual stimulus was presented twice, allowing us to test for adaptation effects in fMRI responses, which typically arise when the same stimulus is repeated (29–31). Previous studies have demonstrated adaptation in face-selective regions with the repetition of pictures of the same face identity as compared with different faces (32–34), and such adaptation is modulated by emotional expression (35). By testing for repetition effects, we could further assess the sensitivity of face-selective areas to individual face identities and emotional expressions.

On the basis of behavioral findings of impaired face recognition in 22q11DS (5,14,15), we predicted an abnormal pattern of response to faces and expressions in social processing networks in these patients relative to control subjects.

Methods and Materials

Participants

Fifteen patients affected by 22q11DS and 16 matched healthy control subjects were recruited consecutively from our clinic and from the general population, respectively. All participants were native French-speaking and Caucasian. Psychiatric evaluation was conducted with standardized semi-structured interviews (Table 1). Five (2 male) of the 22q11DS patients had some psychotic symptoms, consistent with similar rates in previous studies (1,3,36). None of the patients were medicated for these symptoms. Written informed consent was received from all adult participants and parents of participating children and adolescents under protocols approved by the Institutional Review Board of the Department of Psychiatry of the University of Geneva Medical School.

The presence of a 22q11.2 microdeletion was confirmed in all participants with DNA analysis. Deletions were verified and their extent determined by two-color fluorescence in situ hybridization (FISH), with cosmid probes cD0832 and c350, specific for the proximal and distal deletion regions respectively (37).

Materials and Procedures

The visual categorization task consisted of a randomized presentation of photographs of fearful faces, neutral faces, and houses (24 items for each of these three categories, each repeated twice). All photos had the same size (457 × 511 pixels) and appeared on a white background. For presentation during fMRI, stimuli were back-projected onto a screen in front of the scanner with a mirror mounted on the head-coil (visual angle approximately 5.9° × 6.8°). Face stimuli comprised 48 different adult identities (12 neutral women, 12 fearful women, 12 neutral men, 12 fearful men), selected from two standardized sets of photographs, the Karolinska Directed Emotional Faces (KDEF, D.Lundqvist, A.Flykt, A.Öhman, Department of Neurosciences, Karolinska Hospital, Stockholm, Sweden, 1998) and the NimStim face database (<http://www.macbrain.org>), which have been previously validated for emotional ratings in the normal population. Fearful and neutral faces were always from different identities. Two versions of each photograph were presented, each with a different color hue (i.e., increased saturation for either red or blue), to minimize any effects of repeating the same pictorial content while testing for the effects of repeating the same face identity (29,33). Repetitions occurred with a pseudo-random interval of 3–8 intervening stimuli.

Stimuli were presented centrally (duration 500 msec each) in a pseudo-randomized order with a mean stimulus onset asynchrony of 4.8 sec (randomly jittered between 3.8 and 8.8 sec). An additional 30 null trials (longer intervals without any photographs) were intermixed with test trials to provide an appropriate baseline measure (38). All photos were preceded by a fixation cross that remained on the screen for 500 msec. Participants were instructed to categorize each photograph as a “face” or a “house,”

Table 1. Demographics and Medical Data of Control Subjects and Affected Individuals

	Control (n = 16)			22q11DS (n = 15)		
	n	Mean	SD	n	Mean	SD
Age (yrs)	16	15.03	± 5.51	15	15.27	± 4.31
IQ						
Verbal IQ	16	111.69	± 9.48	15	79.6	± 13.61
Verbal comprehension	16	111.13	± 8.44	15	82.8	± 13.25
Performance IQ	16	110.13	± 12.6	15	71.87	± 12.3
Perceptual organization	16	110.25	± 12.27	15	72.4	± 11.18
Full-scale IQ	16	112.56	± 10.86	15	73.8	± 12.39
Gender						
Male	7			5		
Female	9			10		
Psychotic Symptoms						
Yes	NA			5 (2 males, 3 females)		
No	NA			10 (3 males, 7 females)		

IQ was measured with the Wechsler Adult Intelligence Scale III and Wechsler Intelligence Scale for Children III. Psychotic symptoms were determined with the Computerized Diagnostic Interview for Children and Adolescents for individuals younger than 18, the Structured Clinical Interview for DSM-IV Axis I Disorders for adults, and the Psychosis module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime in all individuals. Psychotic symptoms included hallucinations and delusions, but none of the patients received a diagnosis of schizophrenia. None of them was medicated for psychotic symptoms. Control participants were screened for the absence of health, neurological, or psychiatric problems and scored in the normal range on behavioral questionnaires (Child Behavior Checklist and Item Symptom Checklist-90—Revised).

by pressing one button for each category (right vs. left button). The task was designed to ensure equal attention to each stimulus and evoke equivalent performances between the clinical and control groups. To ensure that the task was understood, each participant completed a short practice session before scanning (with a few stimuli that were not used during fMRI). The task was run with E-prime software (Psychology Software Tools, Pittsburgh, Pennsylvania).

fMRI Scanning and Analyses

The MRI data were acquired on a 1.5-T whole-body INTERA system (Philips Medical Systems, Andover, Massachusetts). Structural images were acquired with a three-dimensional gradient-recalled-echo (GRE) T1-weighted sequence (field of view [FOV] = 250 mm, repetition time [TR]/echo time [TE]/Flip = 15 msec/5.0 msec/30°, matrix = 256 × 256, slice-thickness = 1.25 mm), and 239 functional images were acquired with a GRE-echo planar imaging (EPI) sequence (TR/TE/Flip = 2500 msec/40 msec/80°, FOV = 250 mm, matrix = 128 × 128, 30 contiguous 4-mm axial slices).

Functional images were analyzed with the general linear model for event-related designs in SPM2 (Wellcome Department of Imaging Neuroscience, London, United Kingdom; <http://www.fil.ion.ucl.ac.uk/spm>). All images were realigned, corrected for slice timing, normalized to an EPI template (resampled voxel-size of 3 mm), spatially smoothed (8-mm full width at half maximal Gaussian kernel). A high-pass frequency filter (cutoff 120 sec) and corrections for auto-correlation between scans were applied to the time series.

Statistical analysis was performed with the general linear model. Each event type was modeled as a separate regressor convolved with a canonical hemodynamic response function. Movement parameters from realignment corrections were entered as additional covariates of no interest to account for residual movement artifacts after realignment. Six event types were defined, corresponding to each of the critical stimulus conditions (House 1st presentation, Neutral Face 1st presentation, Fear Face 1st presentation, House 2nd presentation, Neutral Face 2nd presentation, Fear Face 2nd presentation). Statistical parametric maps were generated from linear contrasts between conditions in each participant. A second-stage random-effect analysis was then performed with one-sample *t* tests on contrast images obtained in each subject for each comparison of interest. In the between-group analysis testing for group × condition differences, contrast images were entered into a two-sample *t* test. Analyses were performed across the whole brain. Following standard practice (39), focal activations were considered as significant at a voxel level of $p < .001$ (uncorrected, whole brain analysis) with a cluster threshold of more than 5 voxels. Additional standard analyses of variance (ANOVAs) were performed on parameter estimates of activity extracted from clusters with SPSS 14.0 (SPSS, Chicago, Illinois).

Results

Behavioral Data

Subjects with 22q11DS and healthy control subjects showed similar accuracy on the visual categorization task during fMRI (Table 2). Repeated-measures ANOVA did not reveal any significant differences in reaction time [$F(1,29) = .266, p = .6099$] or accuracy [$F(1,29) = 1.026, p = .3194$] between groups for category, facial expression, or repetition.

Table 2. Reaction Time and Accuracy for Faces and Houses in Each Group

	Reaction Time (sec)		Accuracy (%)	
	Mean	SD	Mean	SD
Control Subjects				
First presentation				
Faces	644.1	± 177.5	98.2	± 2.1
Houses	649.1	± 165.2	94.1	± 11
Second presentation				
Faces	639.3	± 195.6	98.4	± 4.6
Houses	653.2	± 175.2	96.2	± 7.5
22q11DS				
First presentation				
Faces	598.3	± 198.9	98.6	± 1.9
Houses	631	± 230.6	90.8	± 13.6
Second presentation				
Faces	579.9	± 201.5	96.8	± 3.8
Houses	631.1	± 237.4	92.3	± 10

Analysis of variance did not reveal any effect of diagnosis. 22q11DS, 22q11.2 deletion syndrome.

Imaging Data

Neutral Faces versus Houses. We first determined brain regions with face-selective responses by contrasting trials with neutral faces to those with houses. A separate analysis for the control group demonstrated a network typically associated with face processing, including lateral FG and occipital visual areas bilaterally (Table 2 and Figure 1). In individuals with 22q11DS, no activation was observed in the lateral FG (even at a lower threshold) or occipital cortex. Only the anterior cingulate cortex (ACC) was activated by this contrast in the clinical group.

A direct comparison of face-related responses between groups (with a voxel-wise two-sample *t* test across the whole brain) confirmed a selective difference in FG bilaterally owing to greater activation in control subjects relative to affected individuals, with this difference predominating on the left side ($p < .001$ uncorrected), although two clusters also showed a difference on the right ($xyz = 42, -48, -21$ and $38, -63, -12$) with a slightly lower threshold (both $Z = 3.18; p < .005$ uncorrected).

In addition, we defined a region of interest (ROI) in lateral FG in both hemispheres, on the basis of face-selective activation in control subjects and then extracted the parameter estimates of activity for this region in both groups. As can be seen in Figure 1, only control subjects showed face-selective responses in the fusiform ROIs, whereas individuals with 22q11DS showed no clear category difference.

Houses versus Neutral Faces

Similar analyses were performed to determine regions with house-selective responses. Separate contrasts in each group revealed a selective activation of bilateral parahippocampal gyri in both patients and control subjects, with a slightly more distributed pattern for other regions in the 22q11DS group (Figure 1). A direct between-group comparison showed enhanced activation in a small part of left parahippocampal and medial FG in control subjects relative to 22q11DS (Table 3). However, despite some differences in absolute magnitude, parameter estimates of activity extracted from parahippocampal ROIs (as delineated in control subjects) showed a similar profile of house-selective responses in both groups.

These results indicate a normal although slightly more distributed pattern of visual responses to houses in 22q11DS patients, in contrast with their lack of face-selectivity in FG.

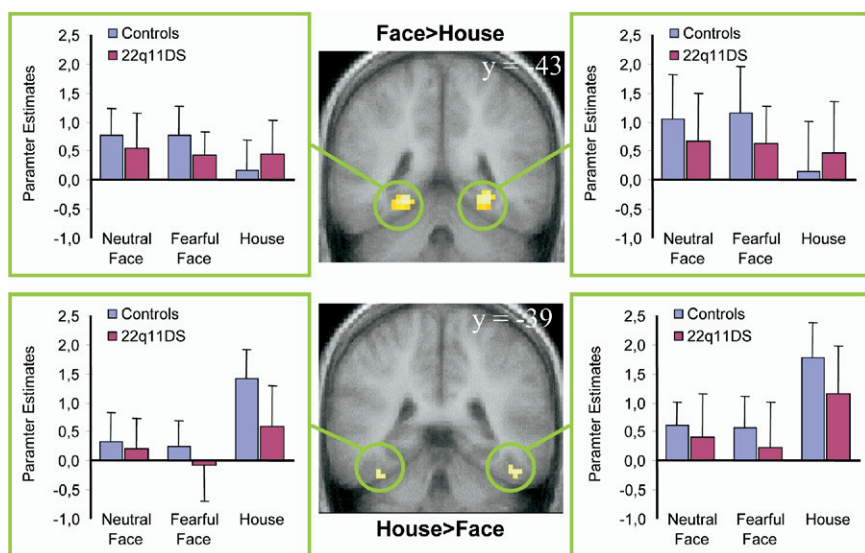


Figure 1. Parameter estimates extracted from clusters identified in control subjects for Face > House (top) and House > Face (bottom) ($p < .001$ uncorrected, bars show the SD). Clusters are superimposed on the mean anatomical images of all subjects (control subjects and 22q11.2 deletion syndrome [22q11DS]). No face selectivity in fusiform cortex is apparent in 22q11DS, but normal house selectivity is found in parahippocampal cortex in each group.

Fearful Faces versus Neutral Faces

We then tested for responses to emotional expression by contrasting fearful versus neutral faces (across first and second presentations) in each group. In control subjects, greater activation to fearful faces was observed in the anterior part of the STS. By contrast, in patients, fearful faces activated the inferior frontal gyrus and superior frontal sulcus (Table 4). No significant main effects for fearful versus neutral expressions were observed in the amygdala or FG for either group (even at low threshold of $p = .01$ uncorrected) when collapsing across repetition trials. However, in control subjects, activation of the amygdala was observed when the first presentation of fearful faces was compared with the first presentation of neutral faces (see subsequent text: Adaptation to Fearful Faces).

Between-group analysis showed greater activation in the ACC in control subjects (similar to the region activated in the 22q11DS group in response to Faces vs. Houses) as well as in a small region of anterior STS ($xyz = -51, -12, -6$; $Z = 3.79$; $p = .001$ uncorrected; $k = 3$ voxels).

Adaptation to Neutral Faces

As expected, a significant effect of repetition (decrease in activity for second vs. first stimulus presentation) was observed for neutral faces in both left and right lateral FG in the control group (slightly more posterior than the peak for Face vs. House) as well as in bilateral medial orbital frontal regions (Table 5). By contrast, the 22q11DS group showed a decrease in activation in the right frontal superior gyrus but no repetition effects in visual cortex. A between-group comparison confirmed this significantly greater adaptation in left lateral FG in the control subjects relative to 22q11DS ($p < .001$).

Adaptation to Fearful Faces

Finally, we examined repetition effects for emotional faces. In the control group, a decrease in activation in the left posterior temporo-occipital junction and right ventro-lateral amygdala was observed with the second presentation of fearful faces (Table 5). No significant repetition effect was observed for emotional faces in FG (even at $p = .05$ uncorrected), unlike the repetition of neutral faces. Again, the 22q11DS group demonstrated a different pattern, with a decrease in activation to repeated fearful faces

in prefrontal regions only. Between-group analysis also confirmed a greater activation in the right amygdala, left middle frontal gyrus, and left inferior temporal gyrus in control subjects.

Parameter estimates of activity from the right amygdala are shown in Figure 2 for each condition and each group. The repetition suppression effect for fearful faces was clearly apparent in control subjects; whereas no consistent effect of emotion or repetition was observed in the 22q11DS group. Repeated-measures ANOVA performed for neutral faces did not reveal any significant main effect of group [$F(1,29) = 1.747$, $p = .1966$], repetition [$F(1,29) = 1.174$, $p = .2875$], or interaction between group and repetition [$F(1,29) = 1.659$, $p = .2079$], whereas ANOVA performed for fearful faces did not reveal a main effect of group [$F(1,29) = .382$, $p = .5415$] but revealed a significant main effect of repetition [$F(1,29) = 9.727$, $p < .005$] and significant interaction between group and repetition [$F(1,29) = 12.439$, $p < .002$]. In keeping with our SPM analysis (Table 5), there was a significant interaction effect in the amygdala ($p < .001$) for group \times repetition for fearful faces.

Relationship to Psychotic Symptoms

Although our sample of affected subjects is relatively small for definite inferences about possible relation to clinical symptoms, we performed an exploratory analysis to compare face-related responses (faces > houses) between 22q11DS patients with or without psychotic symptoms ($n = 5$ and 10, respectively). This exploratory analysis (whole brain, two-sample t test) revealed significantly greater activation in non-psychotic than psychotic patients in left FG ($xyz = -27, -45, -24$, $T = 4.04$, $p = .001$ uncorrected), overlapping with the peak of differences between 22q11DS and control subjects (Table 2), even though both psychotic and non-psychotic differed from healthy control subjects. A similar comparison between non-psychotic and psychotic patients for house-related responses (houses > faces) showed no difference in parahippocampal regions (even at low threshold, $p < .05$ uncorrected). No significant difference was observed for the amygdala.

Table 3. Brain Regions Activated for Faces > Houses and for Houses > Faces

Neutral Faces > Houses	Side	x	y	z	n Voxels	Z Score
Control Subjects						
Lateral fusiform gyrus	L	-39	-36	-27	17	3.81
Lateral occipital gyrus	L	-33	-75	6	10	3.54
Medial occipital cortex	L/R	3	-81	3	27	3.62
Lateral occipital gyrus	R	48	-75	3	32	4.18
Lateral fusiform gyrus	R	48	-39	-24	6	3.64
22q11DS						
Anterior cingulate	R	6	39	-3	9	3.54
Control Subjects > Patients						
Lateral fusiform gyrus	L	-33	-45	-27	9	3.5
Houses > Neutral Faces						
Houses > Neutral Faces	Side	x	y	z	n Voxels	Z Score
Control Subjects						
Middle occipital	L	-33	-93	9	19	3.9
Parahippocampal gyrus	L	-24	-45	-12	122	4.53
Precuneus	R	15	-51	12	13	3.9
Parahippocampal gyrus	R	24	-51	-12	150	4.62
Middle occipital	R	33	-90	24	5	3.45
Middle occipital	R	33	-78	9	5	3.42
Middle occipital	R	36	-78	18	5	3.32
22q11DS						
Central sulcus	L	-57	-21	36	10	3.52
Orbito-frontal cortex	L	-45	21	-9	10	4.1
Middle occipital gyrus	L	-36	-87	9	10	3.68
Central sulcus	L	-36	-33	42	6	3.6
Precentral sulcus	L	-36	-27	57	77	4.86
Parahippocampal gyrus	L	-30	-45	-27	116	4.52
Central sulcus	L	-24	-42	51	7	3.44
Postcentral gyrus	L	-24	-39	63	6	3.3
Precentral gyrus	L	-24	-15	57	17	4.37
Inferior occipital	L	-21	-96	3	25	4.21
Supplementary motor area	L/R	0	-9	51	37	4.14
Middle cingulate	R	6	-30	30	6	3.53
Parahippocampal gyrus	R	27	-39	-21	49	5.03
Frontal superior sulcus	R	30	-9	63	29	3.8
Central sulcus	R	33	-39	57	8	3.5
Inferior occipital gyrus	R	36	-84	6	7	3.3
Middle occipital gyrus	R	36	-84	21	6	3.4
Central sulcus	R	36	-42	42	12	3.72
Precentral sulcus	R	36	-30	66	12	3.59
Angular gyrus	R	39	-60	24	6	3.59
Central sulcus	R	48	-30	42	18	3.66
Supramarginal gyrus	R	57	-18	27	7	4.12
Superior temporal gyrus	R	63	-36	21	5	3.29
Control Subjects > 22q11DS						
Medial fusiform gyrus	R	27	-60	-6	15	3.96

22q11DS, 22q11.2 deletion syndrome. $P < .001$ uncorrected.

Discussion

Face Processing

By using fMRI to probe visual recognition in young individuals with 22q11DS, our study reveals for the first time that, unlike healthy control subjects, these patients do not activate the typical face processing network in response to faces and expressions. In particular, a region in lateral FG corresponding to the “fusiform face area” (FFA), as described by Kanwisher and others (26,27,40), showed a selective deficiency in patients when comparing responses to neutral faces and houses. Activity in lateral FG showed clear category-specificity (faces > houses) in

control subjects but not in patients (Figure 1). Moreover, a lack of repetition effects in response to neutral faces in 22q11DS provided further evidence for abnormal fusiform function in 22q11DS. By contrast, normal repetition-related decreases for neutral faces were observed in posterior FG bilaterally for control subjects (29,35). Taken together, these data converge to indicate a lack of perceptual tuning to faces in visual extrastriate cortex for the 22q11DS group. In addition, inferior lateral occipital regions, corresponding to the putative “occipital face area” (27,34), were also activated by contrasting Faces versus Houses in control subjects but not in patients, although this difference

Table 4. Brain Regions Activated for Fearful Faces > Neutral Faces Across All Repetitions (First + Second Face Presentation)

Fearful Faces > Neutral Faces	Side	x	y	z	n Voxels	Z Score
Control Subjects						
Anterior superior temporal sulcus	L	-51	-12	-6	6	3.83
22q11DS						
Superior frontal sulcus	L	-27	18	57	11	4.07
Inferior frontal gyrus	R	51	24	0	30	4.45
Controls > Patients						
Anterior cingulate	R	15	30	0	6	3.47

22q11DS, 22q11.2 deletion syndrome. $P < .001$ uncorrected.

did not reach conventional significance in a direct between-group comparison.

Impaired fusiform activation in 22q11DS cannot be accounted for by difference in performance or attention to the task. Indeed, similar accuracy and reaction times were obtained in both groups. Likewise, age factors cannot explain differences between control subjects and patients because both groups were carefully matched; and although our participants were generally young, all were older than 10, an age at which children usually show adult-like cortical responses to faces (41), as demonstrated here in our control group. Furthermore, the lack of face-specific responses in the FG in 22q11DS subjects contrasted with their intact pattern of house-specific responses in parahippocampal gyrus, as reported in typically developing individuals (28), indicating that fusiform deficits do not reflect diffuse anomalies in cortical specialization within the temporal lobes. Rather, our results suggest a specific disorder in the development of face processing networks associated with 22q11DS. These findings dovetail with recent behavioral studies showing that 22q11DS is associated with distinctive deficits in face processing (14,15).

This lack of specificity in face processing might be explained either by direct genetic factors promoting face perception skills (42,43) or by the importance of expertise in the tuning of

specialized cortical pathways. According to a “domain general view” of visual recognition (44), weak experience and expertise in processing face stimuli could lead to a deficiency in FFA activity. In line with this view, the ability to distinguish between exemplars belonging to the same visual category arises during a critical period in the development of ventro-temporal visual areas, including the FFA. Similarly, a theory of interactive specialization (45) has been proposed to explain the development of face processing in newborns and infants. Accordingly, some deficits in early orienting of attention to faces (46) might change the effect of experience on neural pruning in face processing pathways and result in abnormal development of visual cortex. Further research is needed to clarify the role of these different mechanisms in the establishment of specialized networks for face recognition in the normal brain and the nature of their impairments in 22q11DS.

Emotion Processing

When comparing neural responses to emotional expressions of faces, we found that fearful faces produced different patterns of activation in 22q11DS and control subjects. Control subjects showed an increased response in anterior STS, a region previously shown to be sensitive to social cues and face expression

Table 5. Brain Regions Showing Repetition-Suppression Effects (First > Second Presentation) for Neutral Faces and for Fearful Faces

	Side	x	y	z	n Voxels	Z Score
Neutral Face Adaptation						
Control subjects						
Inferior frontal gyrus	L	-54	18	0	7	3.76
Lateral fusiform gyrus	L	-39	-66	-21	63	4.45
Lateral fusiform gyrus	R	36	-48	-30	12	3.79
Superior temporal gyrus	L	-51	12	-12	7	3.96
22q11DS						
Superior frontal gyrus	R	27	6	60	14	3.75
Fearful Face Adaptation						
Control subjects						
Post temporo-occipital junction	L	-48	-66	24	15	4.41
Ventro-lateral amygdala	R	33	3	-30	11	4.22
22q11DS						
Middle cingulate	L	-6	-6	33	11	3.58
Middle cingulate	R	18	-18	36	9	3.54
Middle frontal gyrus	R	24	21	24	12	4
Middle frontal gyrus	R	24	42	27	6	3.28
Controls > Patients						
Inferior temporal gyrus	L	-36	33	42	6	3.50
Middle frontal gyrus	L	-33	0	-45	5	3.42
Ventro-lateral amygdala	R	33	3	-33	8	4.09

22q11DS, 22q11.2 deletion syndrome. $P < .001$ uncorrected.

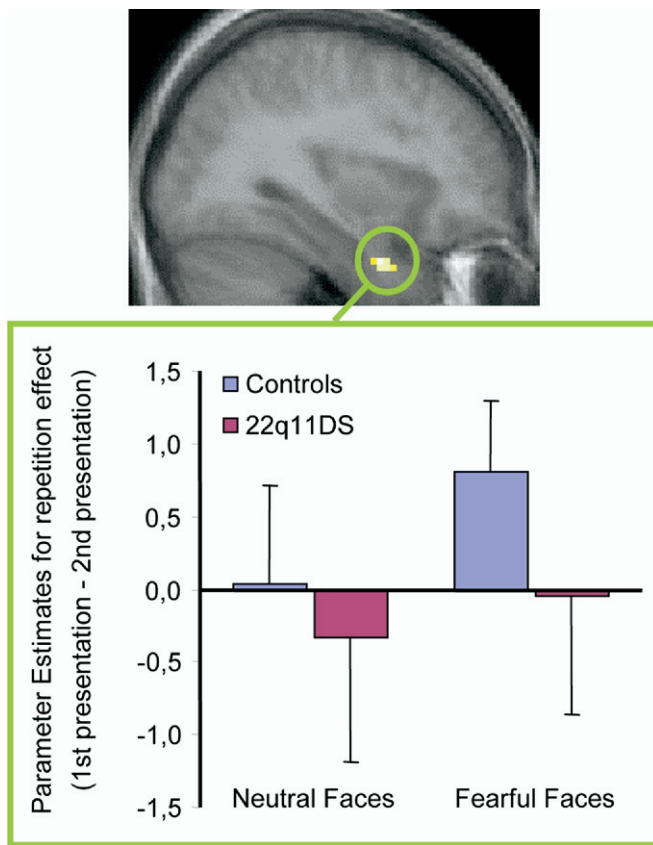


Figure 2. Parameter estimates for the difference between first and second presentation extracted from an amygdala cluster in amygdala ($x, y, z = 33, 3, -30$) identified in control subjects from the Fearful Face adaptation contrast for the first vs. second presentation of fearful faces ($p < .001$ uncorrected). The cluster is superimposed on the mean anatomical images of all subjects (control subjects and 22q11DS). A response to fearful faces on first presentation with subsequent repetition effect suppression for fearful faces is apparent only in control subjects.

more than to face identity (47,48). By contrast, affected individuals demonstrated activation in prefrontal areas not engaged during facial or emotional processing in typically developing individuals (49,50) but no activation of STS. This differential activation of dorsolateral prefrontal areas might reflect some atypical or compensatory cognitive processes during social recognition in 22q11DS. In addition, a direct whole-brain contrast between groups also revealed greater emotional responses in the rostral ACC for control subjects relative to patients, although a similar region was activated by neutral faces in 22q11DS but not in control subjects. Rostral ACC has been associated with the regulation of emotions in studies conducted on both healthy individuals and clinical samples (51,52) and might be abnormally responsive to facial expressions in 22q11DS.

Furthermore, when testing for repetition suppression effects for emotional faces, we found that control subjects exhibited a strong response in the right amygdala to the first presentation of fearful faces, with a reduced response (i.e., adaptation) when the same fearful faces were repeated (i.e., same face identity with same expression but slightly modified colors in picture, see Methods). This pattern is consistent with previous fMRI findings of adaptation in brain areas sensitive to repeated stimuli (29,53) and with habituation of amygdala responses to repeated negative stimuli (54). Critically, however, patients with 22q11DS did not

show a similar pattern of amygdala activity, with no systematic effect of either expression or repetition.

We note that neither the control or 22q11DS groups exhibited significant increases in amygdala activation to fearful versus neutral faces on the second stimulus presentation (or when pooling trials across all repetitions), which contrasts with results from other studies where differential responses to fear still persisted after several repetitions of the same stimulus (25). It is possible that the relatively young and/or broad range of age of our sample might result in distinct patterns of activation to emotional faces, as compared with fMRI studies conducted on typical adults. The neural pattern associated with normal development of emotional face processing might not be observable before mid-adolescence (55). The young age of our participants, coupled with a relatively small sample size and a fast event-related fMRI protocol, might have reduced our ability to detect a more subtle and mature pattern of responses to emotional faces across stimulus repetitions.

Nevertheless, taken together, our results clearly point to significant anomalies in a network of brain areas involved in emotional face processing in patients with 22q11DS, including anterior STS, rostral ACC, and amygdala. Whereas the FG is implicated in the perception of facial identity, both STS and amygdala play a critical role in the analysis of facial expression and the interpretation of social signals, such as gaze and intentional gestures (49,50). The importance of the amygdala in emotional face processing is supported by numerous studies (56,57,58,59), and the basolateral part is particularly implicated during emotional learning (60,61) and judgments of personality from faces (62). Thus, in our study, a lack of initial response and subsequent adaptation to fearful faces in the amygdala in 22q11DS might provide a marker for amygdala and thus social dysfunction in 22q11DS. It remains to be determined whether these anomalies primarily reflect impaired sensitivity to facial emotions or partly result from abnormally high amygdala responses to neutral expressions, as observed in some cases with schizophrenia (63).

Emotional Face Processing in Psychosis

Abnormal face processing has repeatedly been observed in schizophrenia, although few functional imaging studies have been carried out in young at-risk subjects before psychotic symptoms. Some suggested that a lack of specificity in face processing areas, such as FG and amygdala, might contribute to social and affective disturbances in schizophrenia (64,65). Other authors proposed that emotional face processing problems in schizophrenia might be rooted in limbic dysfunction more than perceptual impairments (66–68). In any case, these studies point to some deficits in amygdala that might play a major role in emotional disorders in this disease (69).

In 22q11DS, a few studies have tested for structural alteration of amygdala and reported inconsistent results. Some found an association between volumetric amygdala alterations and psychiatric symptoms in children with 22q11DS, suggesting that structural amygdala anomalies could be a reliable marker for the onset of severe psychiatric disorder (70). Others found preserved structural volumes of the amygdala in a large sample of subjects (71). Nevertheless, functional disorders are not necessarily related to anatomical anomalies, and the current study is the first report using functional imaging to examine emotional face processing in 22q11DS and to provide direct evidence for amygdala dysfunction, with a lack of the initial response and subsequent adaptation to fearful faces normally seen in healthy

individuals. However, in exploratory analyses, we found that patients with psychotic symptoms showed more severe deficits in activation of the FG, relative to non-psychotic patients, but no difference in amygdala, although these data must be taken with great caution, owing to our small sample. Future longitudinal studies might help determine the time-course of facial and emotional processing deficits in relation to symptom onsets.

In conclusion, the current study provides the first fMRI data illuminating the neural bases of face recognition and social impairments associated with 22q11DS. Our results show selective anomalies in brain regions implicated in social function, including a lack of face-selectivity in FG and a lack of modulation by fear expression in amygdala and STS. These data provide evidence for abnormalities in the visual ventral stream in 22q11DS and suggest future avenues for investigating the influence of visuo-perceptual and affective dysfunctions on common psychopathological features of the syndrome.

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