Article

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Abstract

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Reference

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Eye Gaze During Face Processing in Children and Adolescents With 22q11.2 Deletion Syndrome

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The 22q11.2 deletion syndrome (22q11DS), also known as velocardiofacial syndrome (VCFS) or DiGeorge syndrome, is a neurogenetic disorder that affects approximately 1 in 4,000 newborns.[1] Common features of the syndrome include velopharyngeal insufficiency and cardiac problems, two of the most detectable physical characteristics. For almost two decades, 22q11DS has been thought of as a neurogenetic model for understanding psychosis.[2,3]

High rates of many psychiatric disorders are a hallmark feature of 22q11DS through childhood, adolescence, and adulthood.[4] Depression and psychosis in adults, and anxiety in children, adolescents, and adults, constitute the most frequent psychiatric diagnoses in the syndrome. Psychotic symptoms, such as hallucinations and delusions, have been observed in children and adolescents with 22q11DS,[5,6] and are often accompanied by difficulties naming and recognizing their own and others' emotional states, a lack of social relationships and social integration, and high levels of social anxiety.[7,8] Given high comorbidity between anxiety and psychosis,[4,9] anxiety disorders may signal high risk for psychosis in affected individuals. Autistic-like traits also have been frequently observed in the syndrome, especially difficulties with communication and socialization.[7,10] For this reason, clinicians and parents alike are in need of clear markers for measuring and understanding socio-emotional impairments in 22q11DS.

Structural differences in fusiform[11,12] and medial temporal areas[13,14] also indicate abnormal socio-emotional processing and limbic function in 22q11DS. Moreover, recent functional magnetic resonance imaging studies show differential activation patterns during face processing in 22q11DS,[15,16] including pronounced fusiform hypoactivation in psychotic individuals.[16] However, it is still not known how these changes affect the way that individuals look at faces. For this reason, the current study investigates eye gaze during a face-processing task in children and young adolescents with 22q11DS.

At least two types of face processing identified in normal subjects provide a platform for testing and understanding face processing deficits in individuals with atypical development. The first involves featural, or piecemeal, comparisons of the eyes, mouth, and nose on a face. Children appear to be initially better at using featural information, or the fine-grained detection of details, than changes in the configuration of a face (i.e., computing the spacing between features), to recognize differences in identity.[17] Even young school-aged children have been shown to be capable of matching faces with featural changes at adult levels.[18] However, featural processing may not be specific to faces but, rather, used to recognize other types of objects as well.[19]

The second type of face processing, configural processing, refers to a face processing strategy that develops more slowly. Configural processing is unique to faces and refers to a way of recognizing them based on their composition.[19,20] Configural processing can be as simple as differentiating a face from another object using its telltale triangular composition, the eyes above the nose and mouth; or it can refer to a computation of the relationships between facial features, the spatial configuration of a face that is used specifically for differentiating two faces.[21] Once configural processing is mature, adolescents and adults mainly use spatial relationships between features to discriminate between two faces.[18] This gradual preference for configural processing is detected through a disruption in the recognition of inverted faces with configural modifications (inversion effect), initially apparent around 10 years of age and mature during adolescence,[18,22] although some studies have reported evidence for configural processing as early as age 4 years.[23]

The fact that it takes a long time to fully master configural processing (typically developing individuals do not reach adult levels of face processing before adolescence[18]) suggests that it may be more vulnerable in individuals with atypical development. Studies investigating face processing impairments in disorders with atypical cognitive and social development, such as autism, Williams syndrome, Down syndrome, and Turner syndrome, have provided a better understanding of the effects of altered development on featural and configural face processing.[24-27]

Interestingly, disorders associated with deficits in face processing also have frequently shown a lack of attention to the eyes,[28-30] one of the most important areas for recognizing emotional expressions,[31] thus making attention to the eyes a candidate mechanism for exploring impaired social cognition in developmentally atypical individuals. Lack of attention to the eyes, a likely consequence of either changes in the way young babies respond to faces[32] or disruptions that occur later in development,[33] also could partially explain reductions in face-specific cerebral responses in individuals with developmental disorders.[16,34] Indeed, the 70% of time spent on the eyes in typical face exploration appears to optimize face-specific blood oxygen level dependent responses.[35]

Given the predisposition of 22q11DS to psychiatric disorder, we sought to understand the nature of face processing impairments in 22q11DS. We therefore analyzed accuracy and scanpath, the sequence of eye movements used to explore a face, using a version of the Jane Task,[18] an experimental task requiring participants to discriminate between faces that are changed either featurally or configurally. Given the frequency of face processing deficits in conditions associated with mental retardation, individuals with 22q11DS were compared with age-matched healthy controls, as well as individuals with "idiopathic" developmental delay. Based on differential functional responses to faces,[16] we hypothesized that the 22q11DS group would be less accurate at featural and configural processing than both control groups. Furthermore, the developmental complexity of configural processing led us to expect pronounced configural processing impairments in 22q11DS. In addition, given frequent socio-emotional impairments, we expected atypical exploration of face stimuli in 22q11DS, with less time spent on the eyes.

METHOD

Participants

Children and Adolescents with 22q11.2 Deletion Syndrome. A total of 26 individuals with 22q11DS (17 female and nine male; aged 8 to 15 years, mean age 12.36 years) participated in the study. These individuals were recruited through French-speaking parent associations and were tested in our research laboratory for an ongoing, longitudinal study. The 22q11.2 deletion was confirmed using DNA polymorphism analysis based on short sequence repeats or by fluorescence in situ hybridization performed on metaphase spreads spanning the deleted region. During a clinical evaluation with a child and adolescent psychiatrist that

TABLE 1 Demographic Characteristics of Study Subjects

Measure	Control (*N* = 22)			DD (*N* = 17)			22q11DS (*N* = 26)			
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*F*
Age (y)	22	12.41	2.30	17	11.15	2.72	26	12.36	1.92	1.855
IQ										
Full-scale	22	110.50	11.99	17	68.35	10.20	26	74.19	11.84	83.511***
Gender										
Male	14			10			9			
Female	8			7			17			
BFRT	22	43.23	3.29	15	37.87	4.55	26	36.35	3.67	20.905***
CBCL										
Total	22	44.64	10.82		NA	NA	26	59.85	8.48	29.807***
Internalizing	22	46.27	9.17		NA	NA	26	58.88	11.23	17.733***
Externalizing	22	45.77	10.59		NA	NA	26	51.35	8.25	4.200*
RCMAS										
Total	22	43.73	7.85	17	51.24	14.05	26	52.46	10.00	4.484*
Physiological	22	8.14	1.96	17	10.41	3.16	26	10.69	2.41	7.048**
Worry	22	8.86	2.08	17	10.00	3.54	26	9.81	3.10	.907
Social	22	8.91	1.90	17	10.65	3.62	26	11.35	2.30	5.417**
Lie	22	10.00	3.61	17	11.47	2.50	26	11.42	3.86	1.257

	22q11DS (*N* = 26)	
	n	%
Clinical[a]		
Attention	11	42
Anxiety	13	50
Depression	7	27
Psychosis[b]	10	38

Note: Full-scale IQ was measured using the Wechsler Intelligence Scale for Children (WISC–III) for 22q11DS and control participants, and the WISC-IV for DD (developmentally delayed) participants. BFRT = Benton Facial Recognition Test Long Form (raw scores 0 to 54); CBCL = Child Behavior Checklist; RCMAS = Revised Children's Manifest Anxiety Scale.

[a]*Percentage of 22q11DS patients with clinical levels of attention problems, an anxiety disorder, or depression (DSM-IV criteria).*

[b]*Presence of hallucinations or delusions or both.*

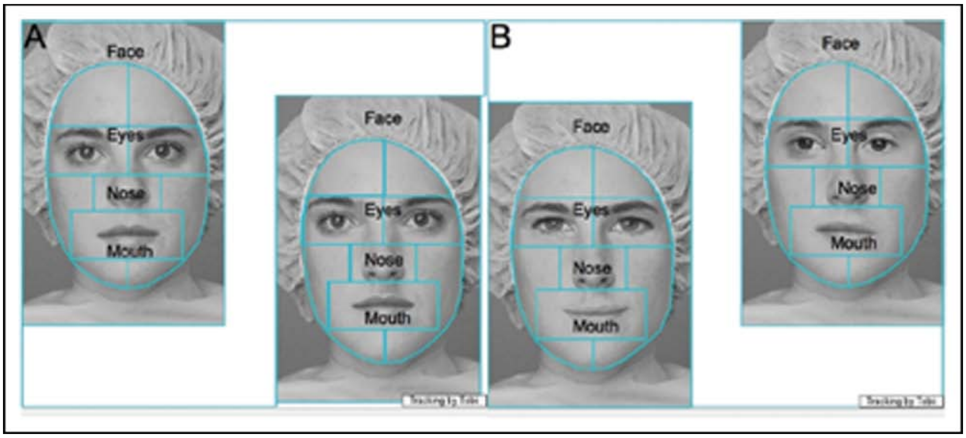
*$p \le .05$; **$p \le .01$; ***$p \le .001$.

included an assessment of psychiatric disorders, but not autism (detailed methods in Green et al.[4]), psychotic symptoms of some kind, either hallucinations or delusions or both, were detected in 38% of the group (10 of 26 individuals). This is commensurate with data in a previous publication,[6] and slightly less than previously reported in a sample of adolescents and adults.[5] Rates of anxiety, depression, and psychosis in the 22q11DS participants are given in Table 1.

Children and Adolescents with Idiopathic Developmental Delay. A total of 17 individuals with "idiopathic" developmental delay (DD; seven female and 10 male; age 8 to 15 years, mean age 11.15 years) were recruited through contacts with special education sites associated with the Service Médico-Pédagogique in Geneva, Switzerland. Individuals with Rett syndrome and FRAXA1 were excluded, as well as individuals with malformations and birth defects. They were evaluated on-site at their school facilities. This group was collected as an IQ-matched control group for certain experimental tasks administered to the 22q11DS patients, and was group matched for age and IQ with the 22q11DS group.

Typically Developing Children and Adolescents. A total of 22 typically developing individuals (eight female and 14 male; age 8 to 15 years, mean age 12.41 years) participated in the study. They were group matched for age with the 22q11DS group. Individuals were recruited through public schools and announcements in the Geneva community. Potential participants were first screened for an absence of neurological, psychiatric problems, and learning disabilities during an interview over the phone and then again through a parent report of behavior (CBCL) and a medical and developmental history questionnaire

FIGURE 1 Examples of (A) Configural Different and (B) Featural Different stimuli, with labeled regions of interest.



completed before their visits. All individuals were tested at our research laboratory.

Demographic details about the groups, including Full-Scale IQ scores, are listed in Table 1. Written informed consent was received from all 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, Switzerland.

Assessment Instruments

Jane Task. The Jane Task[18] is a face discrimination task for assessing featural and configural face processing. The stimuli in the task consist of an original face (Jane) and eight manipulated versions of that face (her sisters), created using a technique by Freire et al.[36] Four of the versions were created by replacing the eyes and mouth with those of other females (Featural set) and the other four were created by moving the eyes up, down, closer together or farther apart, and by moving the mouth up or down (Configural set). In the task, a fixation cross first appeared at the screen's center point (2 s), participants were told to watch the 1 × 1-cm fixation cross until two of the face stimuli were presented side by side in an offset configuration that randomly swapped sides (Figure 1). The faces remained on the screen until the participant answered whether the faces were the "same photo" or "different photos." A total of 30 trials using faces from the Configural set were followed by 30 trials using faces from the Featural set; half of the trials were comparisons of identical faces and half were comparisons of different faces. Trials were presented in a fixed randomized order within each condition.

The task was programmed and administered in Clearview 2.6.3 software (www.tobii.com) on a Tobii 1750 eye tracker with a 17-inch display with a maximum resolution of 1,280 × 1,024 pixels, and a sampling rate of 60 Hz. The Tobii machine can tolerate moderate head movement at 60 cm in front of the device, which is why participants were positioned at 60 cm ± 10 cm from the screen. Before beginning the task, participants did a five-point calibration procedure, which consisted of following a dark gray point on the screen with both eyes. Calibration was repeated until each participant hit each of the five points with both eyes. During the task, fixation points were calculated when gaze points lasted at least 100 ms and fell within a circle encompassing 30 pixels. Task stimuli were superimposed on a white background. Responses were collected via two color-coded juxtaposing keys on the keyboard. Before the task, standard instructions were given, and participants were instructed to respond as quickly as possible. Several practice trials were then presented and discussed aloud with the examiner to confirm each participant's comprehension of the exercise. All participants showed sufficient understanding of the experiment (four consecutive correct answers that were correctly identified aloud as "same" or "different" by the participant in addition to a correct keyboard response) to proceed to the actual task.

Behavioral Questionnaires. The Benton Facial Recognition Test (BFRT)[37] was administered to screen for the ability to match unfamiliar faces. This 22-item test consists of six items for which a participant must identify one other photo of the target person, and 16 items for which a participant must identify three photos of the target person.

The Child Behavior Checklist (CBCL)[38] is a parent-report questionnaire designed to assess several areas of behavior and adjustment. It is composed of three main factors: Total Behavior Problems, Externalizing Behavior Problems, and Internalizing Behavior Problems. CBCL questionnaires were available only for the 22q11DS and typical control groups, and were completed by parents in the week before the evaluation.

TABLE 2 Average Accuracy and Standard Deviations for Jane Task

	Control (*N* = 22)		DD (*N* = 17)		22q11DS (*N* = 26)		
	Mean	SD	Mean	SD	Mean	SD	F
CD	61.8%	31.2%	51.0%	32.7%	36.9%	22.5%	4.610[a]
FD	97.6%	3.9%	86.3%	21.4%	88.7%	9.0%	4.700[a]
Same	87.7%	15.3%	76.5%	20.8%	78.2%	19.5%	2.244

Note: CD = Configural Different trials; DD = developmentally delayed participants; FD = Featural Different trials.
[a]Significant main effect after Bonferroni correction (p < .016).

The Revised Children's Manifest Anxiety Scale (RCMAS)[39] is a self-report instrument for assessing anxiety in children and adolescents 6 to 19 years old. Participants completed the RCMAS before the cognitive evaluation. The RCMAS provides four T scores (Physiological Anxiety, Worry/Oversensitivity, Social Concerns/Concentration, and Lie) in addition to a Total Anxiety T score.

Data Analysis

Individual data were first examined to verify that subjects understood the task. Stimuli were then divided into three conditions: Featural Different trials, Configural Different trials, and Same trials (the Featural or Configural trials with two identical faces), given that the cognitive processes underlying the discrimination of different faces and matching between identical faces may be different.[25] Group distributions were then checked for normality and heterogeneity of variance. Descriptive data (mean and SD) are listed in Tables 2 and 3.

Multivariate analysis of variance (MANOVA) was run in SPSS Statistics 17.0 for Mac with diagnosis as the fixed factor and percent accuracy for the three conditions (Featural Different, Configural Different, and Same) as the three dependent variables. Six additional MANOVA with a similar structure were then run with group as the fixed variable and (Areas of

TABLE 3 Regions of Interest: Percentage of Time Spent on Features Relative to Time Spent on Faces

	Control (*N* = 22)		DD (*N* = 17)		22q11DS (*N* = 26)		
	Mean	SD	Mean	SD	Mean	SD	F
CD							
Face[a]	93.9%	2.7%	90.6%	7.3%	91.1%	11.1%	NS
Traits[b]	90.6%	13.7%	85.3%	11.2%	79.8%	20.2%	NS
Eyes	59.3%	27.6%	62.6%	21.2%	36.8%	22.7%	7.759[c]
Nose	16.8%	17.7%	12.7%	12.5%	15.1%	10.5%	NS
Mouth	14.5%	14.8%	10.0%	13.4%	27.9%	22.7%	5.863[c]
FD							
Face[a]	89.5%	3.0%	90.4%	5.1%	91.5%	5.7%	NS
Traits[b]	91.4%	19.7%	85.8%	18.5%	84.3%	18.0%	NS
Eyes	70.8%	28.7%	61.1%	25.0%	35.4%	29.5%	10.115[c]
Nose	10.9%	14.2%	11.7%	12.1%	12.3%	9.5%	NS
Mouth	9.7%	12.5%	13.0%	14.9%	36.6%	29.8%	10.872[c]
Same							
Face[a]	100%	.014%	100%	.025%	100%	.042%	NS
Traits[b]	90.9%	11.9%	85.8%	13.0%	82.7%	16.7%	NS
Eyes	60.3%	22.6%	61.0%	17.9%	38.3%	23.7%	8.023[c]
Nose	16.5%	13.2%	12.6%	9.5%	16.3%	9.6%	NS
Mouth	14.1%	11.8%	12.2%	11.0%	28.1%	20.3%	7.060[c]

Note: NS denotes that main effect was not run because gateway multivariate analysis of variance (MANOVA) was not significant. CD = Configural Different trials; DD = developmentally delayed participants; FD = Featural Different trials.
[a]Time spent on faces divided by total time on image.
[b]Time spent on facial features (combined eyes, nose, and mouth areas) divided by total time on faces.
[c]Significant main effect after Bonferroni correction (p < .016).

interest (AOI) variables for the three conditions (FD, CD, and Same) as the dependent variables. The dependent variables in these MANOVA were the following (each model included the FD, CD, and Same conditions): overall time on stimuli (faces + background area), percentage of time on the faces, percentage of time on the facial features, percentage of time on the eyes, percentage of time on the mouth, and percentage of time on the nose. Wilks' Lamda criterion was used to determine whether the MANOVA models were significant. For significant MANOVA, univariate ANOVA with a Bonferroni correction (three dependent variables, $p < .016$) were used to follow up the effect of diagnosis on each condition. Differences between groups were then reported according to Bonferroni post hoc tests in SPSS ($p < .016$) if the corresponding univariate ANOVA was significant.

Linear regressions were run separately for each subject group to evaluate the effects of age, FSIQ, RCMAS T scores, and CBCL T scores. One variable at a time was tested to predict accuracy or time on the eyes.

RESULTS

The groups were first compared on the Benton Facial Recognition Test (BFRT). A disability to recognize multiple photos (with changed lighting and perspective) of unfamiliar faces was observed among 22q11DS and DD groups compared to typically developing controls. The 22q11DS group matched a comparable number of faces as the DD group (Table 1). The DD and 22q11DS groups also demonstrated lower IQ scores and higher levels of anxiety than controls (Table 1).

Jane Task: Accuracy

All data were initially examined to ensure that subjects fell within two standard deviations of their group on accuracy for the three conditions of the Jane Task. All three groups performed best on Featural Different, Same, then Configural Different trials, respectively (Table 2). MANOVA testing the effect of group diagnosis on accuracy on the three conditions of the task was significant ($F(6, 120) = 3.440$, $p = .004$), with group differences on Configural Different ($F(2, 64) = 4.610$, $p = .014$) and Featural Different ($F(2, 64) = 4.700$, $p = .013$). Bonferroni post hoc tests did not reveal differences between the DD and 22q11DS groups for either Configural Different and Featural Different trials. However, both the DD and 22q11DS groups were less accurate than controls on Featural Different trials, and 22q11DS participants also were less accurate than controls on Configural Different trials. Age of participants did not predict accuracy for any of the conditions in any of the three diagnostic groups.

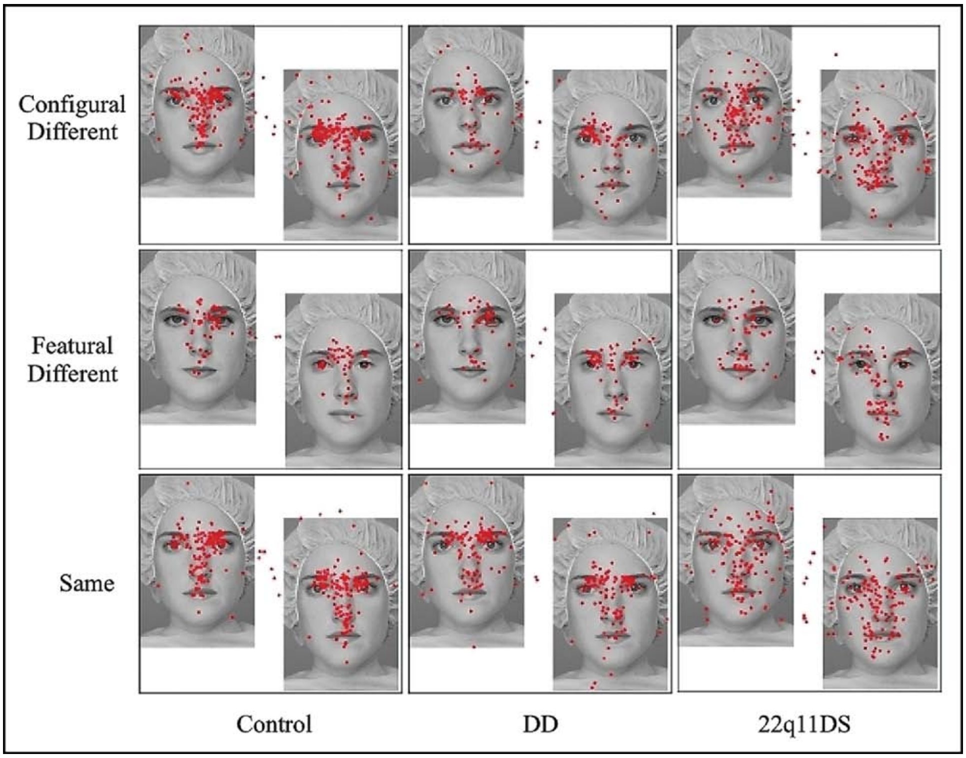
Jane Task: Areas of interest

Before analyzing specific regions of the face, we used MANOVA to investigate whether the groups differed on time looking at task stimuli. The groups spent similar amounts of time exploring the stimuli across the three conditions. Subsequent MANOVA suggested that the groups also spent similar percentages of time on the face (out of the total time they spent on the stimuli) across conditions (Table 3). After these initial explorations, we divided the stimuli into regions of interest (Figure 1) and calculated time spent on regions of the face divided by total time on the face for each individual. MANOVA suggested that the groups spent equivalent time on the facial features (Eyes, Nose, and Mouth together) across conditions (Table 3).

Despite the fact that subjects spent similar time on faces and facial features, MANOVA showed a significant effect of subject group on the amount of time spent on the eyes by condition ($F(6, 120) = 4.174$, $p < .001$) (Table 3). There were main effects of diagnostic group on time spent on the eyes for all three conditions of the task (Table 3). Follow-up tests revealed that the 22q11DS group spent less time on the eyes than the other two groups for all three conditions (Figure 2). To understand whether age affected time on the eyes, we regressed age on time on the eyes in each of the three groups. Age contributed significantly to the percentage of time dedicated to the eyes during Configural Different trials in the control group only ($F(1, 20) = 7.957$, $p = 0.011$, $R = 0.534$, $R^2 = 0.285$).

Subsequent MANOVA showed the groups also differed on the amount of time they spent on the mouth area across conditions ($F(6, 120) = 3.838$, $p = .002$). Univariate ANOVA with Bonferroni correction showed main effects between diagnostic groups for all three conditions (Table 3). Post hoc tests showed that the 22q11DS group spent more time on the mouth than the other two groups during all stimulus conditions. MANOVA did not show differences in the time spent on the nose between groups during any of the three conditions (Table 3). Age did not contribute to the percentage of time on the mouth during any of the conditions in any of the three groups.

FIGURE 2 Participants' fixations on an example image from each of the three conditions.



Predictors of Jane Task Performance

We subsequently explored the contribution of intellectual functioning to the differences observed in accuracy and scanpath. First, we checked for a relationship between Full-Scale IQ and percentage of time on the eyes and accuracy. IQ contributed to the amount of time on the eyes in only the 22q11DS group during all three conditions (CD: B = 0.008, F = 4.605, p = .042, R^2 = 0.161; FD: B = 0.012, F = 6.786, p = .016, R^2 = 0.220; Same: B = 0.009, F = 6.943, p = .015, R^2 = 0.224). Higher IQ scores correlated with more time looking at the eyes. No significant relationships were detected between IQ and time looking at the eyes in the other two groups, or between IQ and accuracy on the task.

Given that anxiety impairs the processing of social stimuli[40] and is the most frequent psychiatric diagnosis throughout the lifespan in 22q11DS,[4] we were interested in how anxiety may relate to time on the eyes. All four domains from the RCMAS were related to less time on the eyes during Configural Different trials in the 22q11DS and DD groups. Lower anxiety scores were related to more time looking at the eyes. We did not observe a relationship between anxiety and time on the eyes in controls (Table 4). Similarly, Internalizing behavior problems as measured by the CBCL appeared to be related to time on the eyes during Configural Different trials in the 22q11DS group. More behavior problems contributed to less time on the eyes (Table 4).

DISCUSSION

In the current eye gaze study of face processing, 22q11DS patients resembled the DD group in terms of accuracy on the task but not in terms of visual exploration. 22q11DS patients spent much less time on the eyes, and more time on the mouth, than either of the other two groups. In addition, IQ contributed to time on the eyes in 22q11DS only, and higher anxiety (measured via self-report) and internalizing behavior problems (parent report) contributed to less time on the eyes and more time on the mouth in 22q11DS and DD participants. These results provide evidence for abnormal exploration of faces in the syndrome, and suggest that time spent on the eyes may contribute to face processing difficulties and may interact with anxiety levels to exacerbate socio-emotional dysfunction in affected individuals.

TABLE 4 Predictors of Time Spent on Eyes during Configural Different Condition

Dependent and Predictor Variables	Control (*N* = 22)				DD (*N* = 17)				22q11DS (*N* = 26)			
	B	F	*p*	R^2	*B*	F	*p*	R^2	*B*	F	*p*	R^2
Eyes, CD												
RCMAS Total	0.002	0.068	.797	0.003	−0.009	7.753*	.014	0.341	−0.010	6.017*	.022	0.200
RCMAS Phys	0.032	1.095	.308	0.052	−0.034	5.162*	.038	0.256	−0.036	4.016	.056	0.143
RCMAS Worry	0.015	0.252	.621	0.012	−0.033	6.723*	.020	0.309	−0.027	3.796	.063	0.137
RCMAS Social	−0.009	0.073	.790	0.004	−0.027	4.039	.063	0.212	−0.040	4.711*	.040	0.164
CBCL Total	−0.005	0.651	.429	0.032	NA	NA	NA	NA	−0.010	3.875	.061	0.139
CBCL Int	−0.005	0.645	.431	0.031	NA	NA	NA	NA	−0.010	7.019*	.014	0.226
CBCL Ext	−0.002	0.115	.738	0.006	NA	NA	NA	NA	−0.004	.615	.441	0.025

Note: Too few Child Behavior Checklist (CBCL) questionnaires were returned in the developmentally delayed participants (DD) group (n = 5) for analysis. CD = configural different; DD = developmentally delayed participants; Ext = externalizing; Int = internalizing; Phys = physiological anxiety; RCMAS = Revised Children's Manifest Anxiety Scale.
*$p \le .05$. **$p \le .01$. ***$p \le .001$.

Both 22q11DS and DD subjects demonstrated featural and configural impairments and a lack of improvement in featural and configural face processing with age compared with typically developing controls. Intellectual delay or perceptual deficits may make configural processing and related cognitive abilities more vulnerable in participants with mild mental retardation (22q11DS and DD groups in the current study). A difficulty estimating distance between stimuli[41] has been previously demonstrated in individuals with 22q11DS, which may hamper individuals' ability to perceive changes in configural spacing. Configural processing impairments have been observed in other neurodevelopmental disorders with impaired visual perception, such as autism[42] and Williams syndrome.[25] Although these impairments may be driven by different underlying processing biases between disorders,[27] they probably all affect face processing to some degree. Intact configural processing is integral to the detection of emotional expressions in faces,[43,44] suggesting that a more "local," or featural, cognitive processing style also could contribute to the socio-emotional problems documented in autism, 22q11DS, and Williams syndrome.[16,45,46]

However, although accuracy on the task was similar, the 22q11DS group spent less of their time on the eye region of the face and more time on the mouth region than the DD group. The importance of the eyes for emotion recognition and functional activity in ventral-occipito-temporal cortex and amygdala has been demonstrated both in individuals with neurodevelopmental disorders, especially autism,[27,28,47] as well as in typically developing individuals.[31,35] Senju and Johnson recently put forward a theory of how enhanced brain activity associated with eye contact may modulate responses to faces,[48] indirectly suggesting mechanisms by which reduced exploration of the eyes in 22q11DS may explain fusiform hypoactivition during face processing.[16] Their "Fast-track modulator model" proposes that early subcortical and later top-down responses interact and modulate cortical response to faces. In 22q11DS, there is evidence for changes to both subcortical networks and top-down motivation and demands. Specifically, subcortical alterations in the pulvinar[49] and the amygdala[14] may reduce salience of the eye area, changing facial preferences in infants with 22q11DS and thereby limiting development of subcortical and cortical face processing networks.

There also is evidence for reduced top-down responses to faces in 22q11DS. Affected individuals are frequently bothered by social phobia and anxiety disorders[4] and display frequent socialization and communication disorders[7] that are characterized by withdrawal, shyness, and immaturity. Another recent study reported a high incidence of autism among 22q11DS patients.[10] Less processing of the eye region was recently related to social aloofness in parents of autistic children, suggesting that eye avoidance may be related to certain behavioral traits[50] in 22q11DS, or alternatively, to a lack of strategy.[51] Of the many behavioral traits in 22q11DS that are likely related to a lack of attention to the eyes, our results imply that anxiety problems contribute in individuals with impaired intellect (22q11DS and

DD participants), suggesting that, in general, individuals with more anxiety spend less time on the eye region. This idea is commensurate with a recent study showing that the duration of fixation on the eyes in autistic individuals is correlated with their level of anxiety but not their severity of autism.[52]

The present study introduces possible factors that may contribute to aberrant social or psychiatric behavior in 22q11DS and raises some new questions. We observed differences in time on the eyes during a discrimination task using neutral faces; however, it is still unclear how these processing preferences contribute to the unique psychiatric phenotype in the syndrome. For example, decreased time on the eyes has been detected in other developmental syndromes, without resulting in higher rates of psychosis.

This study has limitations that can inform future studies. First, we focused on a limited age range to reduce developmental variance between our groups and to concentrate on the period when face processing changes most significantly. However, this choice limited our ability to perform comparisons between age groups, which would have been informative in terms of completing our understanding of the full trajectory of abnormal face processing development in the syndrome. To answer this question, we are currently collecting longitudinal data that will allow us to observe developmental changes in face processing and scanpath. Second, asking participants to make a judgment about the two faces may have influenced our results. A recent study[53] did not observe more time on the mouth in a sample of autistic individuals, and hypothesized that this may be because participants did not need to discriminate or make judgments about the faces as in previous studies. Perhaps looking at the mouth is a compensatory way of looking for supplementary verbal information. However, the fact that the percentage of time on the eyes did not differ by difficulty between conditions in the DD and 22q11DS groups argues against this hypothesis. Third, our clinical evaluation did not permit us to detect autism disorders in our 22q11DS group, so we were unable to determine how related our results may be to autistic-like traits in the syndrome. Future studies will have to further examine the overlap between autism and 22q11DS.

In summary, the current report provides evidence for face processing deficits in 22q11DS, a syndrome with documented social impairments and a pronounced risk of psychiatric disorder. A lack of attention to the eyes in the syndrome suggests an avenue by which perceptual awareness and social interactions may diverge from that in developmentally delayed controls, showing that scanpath is probably not dependent on intellectual function. Previous studies have proposed neglect of the eyes as a possible endophenotype for autism[54]; however, given the results of our study, we argue that the eye-time reduction is not specific to autism but is also present in syndromes such as 22q11DS. &

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