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Visual processing of complex social scenes in 22q11.2 deletion syndrome: Relevance for negative symptoms

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ABSTRACT

Current explanatory models of negative symptoms in schizophrenia have suggested the role of social cognition in symptom formation and maintenance. This study examined a core aspect of social cognition, namely social perception, and its association with clinical manifestations in 22q11.2 deletion syndrome (22q11DS), a genetic model of schizophrenia.

We used an eye-tracking device to analyze developmental trajectories of complex and dynamic social scenes exploration in 58 participants with 22q11DS compared to 79 typically developing controls.

Participants with 22q11DS showed divergent patterns of social scene exploration compared to healthy individuals from childhood to adulthood. We evidenced a more scattered gaze pattern and a lower number of shared gaze foci compared to healthy controls. Associations with negative symptoms, anxiety level, and face recognition were observed.

Findings reveal abnormal visual exploration of complex social information from childhood to adulthood in 22q11DS. Atypical gaze patterns appear related to clinical manifestations in this syndrome.

1. Introduction

Psychotic symptoms fall along two main dimensions, namely, positive and negative symptoms (Crow, 1980). Negative symptoms are defined as diminished behaviors, including five clinical manifestations: apathy, avolition, social withdrawal, blunted affect and alogia. In 22q11.2 deletion syndrome (22q11DS), a neurogenetic disorder representing a model of schizophrenia, negative symptoms are particularly predominant, as they are present in approximately 60–80% of 22q11DS individuals (Schneider et al., 2018; Stoddard et al., 2010). Although negative symptoms represent a core feature of the 22q11DS profile, the psychological mechanisms leading to their emergence remain unclear.

1.1. Social cognition and negative symptoms

Social cognition is defined as the "mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions and behaviors of others" (M. F. Green et al., 2015) . New explanatory models of negative symptoms have suggested that social cognition is an important factor underlying the clinical expression of negative symptoms (M. F. Green et al., 2015). According to the NIMH workshop on social cognition in schizophrenia as social cognition sustains social competences and social functioning. Difficulties in such processes thus might interfere with social motivation/drive (M. F. M.F. Green et al., 2008). While difficulties in social motivation will lead to social withdrawal, social drive impairments will lead to avolition both been described as negative symptoms.

1.2. Social perception

Social cognition is not a unitary construct and encompasses at least four distinct components: social perception, emotion processing, theory of mind, and attributional bias (M. J. M.J. Green et al., 2008). Previous findings have mainly examined the association between negative symptoms and "higher order" socio-cognitive abilities, such as theory of mind, and found conflicting results (Norkett et al., 2017). However,

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Table 1
Demographic information for 22q11DS and healthy control participants for the first available time point.

			Diagnostic group		Comparison	
			22q11DS	Controls	Anova	P-value
N			58	79		
Age			15.5 (4.8)	15.6 (4.7)	0.017	0.898
Gender (% of female)			49.3	47.5	0.005	0.946
Full-scale IQ			69.8 (12.6)	109 (12.8)	387.6	<0.001
RCMAS			23.7 (23.2)			
Benton face			39.8 (10)	45 (4.5)	19.95	<0.001
Emotion recognition			56.37 (10.4)	67.37 (7.34)	6.59	<0.001
Psychotic symptoms	Categories	PANSS positive	12 (5.2)			
		PANSS negative	21.5 (7.6)			
Psychiatric diagnosis (N (%))		Major depression disorder	5 (7%)			
		Specific phobia	10 (13%)			
		Social phobia	3 (4%)			
		Generalized anxiety disorder	4 (5%)			
		Obsessive compulsive disorder	1 (1%)			
		ADHD	19 (25%)			
		Oppositional defiant disorder	1 (1%)			
		Schizophrenia	1 (1%)			

there is a paucity of studies focusing on social perception, a "lower order" core process that supports the other aspects of social cognition (Allison et al., 2000).

1.3. Social perception in 22Q11DS

One of the most ecological ways to assess social perception is by using the eye-tracking method. During social interactions, our gaze is directed toward relevant social information. The quality of our gaze exploration and the proportion of information encoded during social interactions are therefore crucial for complex social cognition, such as decoding emotions or inferring mental states. Divergent gaze exploration of social information could thus lead to disrupted social interactions and to the emergence of negative symptoms, such as social withdrawal, apathy and/or avolition.

In 22q11DS, face perception has been relatively well characterized, whereas a lack of investigation of complex social cues perception has been emphasized (Norkett et al., 2017). Eye-tracking studies investigating the processing of face-related information (See Norkett et al., 2017, for a review) showed that individuals with 22q11DS display atypical scanpath, characterized by shorter scanpath length, fewer fixations and less time spent on relevant facial features (eyes, nose, mouth) compared to typically developing individuals (Glaser et al., 2010, Campbell et al., 2010; Franchini et al., 2016; K. McCabe et al., 2011; K. L. McCabe et al., 2013; Zaharia et al., 2018). Moreover, higher anxiety and internalizing problems have been associated with reduced time spent on the eyes (Glaser et al., 2010), suggesting that anxiety, a common feature of the 22q11DS phenotype, might also impact visual exploration of social information. Furthermore, Zaharia et al. (2018) showed that increasingly altered development of configural processing with age in 22q11DS was associated with negative symptoms severity. An additional study reported an atypical pattern of exploration for both face and non-face stimuli compared to controls, suggesting a general visual processing deficit in 22q11DS (K. McCabe et al., 2011). Thus, clear evidence of abnormal visual processing of face information has been identified in 22q11DS, as well as significant association with several aspects of the 22q11DS phenotype. Most eye-tracking studies conducted in 22q11DS used static stimuli (Campbell et al., 2010; Glaser et al., 2010; K. McCabe et al., 2011; K. L. McCabe et al., 2013). However, social interactions are highly dynamic phenomena (Alves, 2013), which questions the ecological validity of existing findings. One study has explored visual scanning of dynamic social stimuli in 22q11DS and found that, despite a different scanpath compared to healthy controls, a comparable accuracy in emotion recognition was observed (Franchini et al., 2016). Another potential limitation from previous studies is the exclusive use of face pictures. In everyday life, the processing of social information is not only restricted to other individual's faces but also includes body movements (gait, posture) and additional contextual elements of a social situation (M. J. M.J. Green et al., 2008). Thus, the way individuals with 22q11DS explore complex social information and its putative relationship with socio-cognitive processes and negative symptoms has yet to be thoroughly examined. Another important point is that social exploration is a complex phenomenon that is improving throughout the course of development. Despite that, studies conducted in 22q11DS so far did not compare results between age bins. Thus, the developmental stage at which trajectories of social exploration in 22q11DS diverge from typical individuals and might contribute to the emergence of negative symptoms remains largely unknown. The majority of eye-tracking studies extracted parameters on pre-defined regions of interest (Beedie et al., 2011). However, from an ecological point of view, the use of data-driven analyses directly allows a more thorough characterization of the visual behavior beyond the pre-defined inputs (Jianu & Alam, 2018).

1.4. Hypothesis

In our study, we quantified visual exploration of complex social scenes using a data-driven approach (Kojovic et al., 2020).

(1) We compared developmental trajectories of social scenes exploration using a longitudinal design with a total of 173 timepoints obtained from 58 individuals with 22q11DS aged between 6 and 27 years and 79 healthy controls (HC). The HC group was used to define a frame-by-frame "norm" of visual exploration on the three scenes that involved a varying number of characters (1–3). We focused on a moment-to-moment gaze divergence in 22q11DS compared to the normative gaze distribution.
(2) By leveraging longitudinal data, we further aimed to identify a specific time window for the onset of divergence in social visual exploration.
(3) After controlling for the effect of potential confounds, we investigated the relation with clinical variables. Taking into consideration cognitive level, anxiety and attention difficulties, we hypothesized that individuals with 22q11DS would show a divergent pattern of visual exploration of social cues compared to controls and a more divergent pattern of exploration for scenes with higher social complexity.

Table 2
Longitudinal data available per time point.

Number of individuals having:	1 time point	2 time points	3 time points	Total number of timepoints
22q11DS	58	14	2	74
Controls	79	19	1	99
All	**138**	**32**	**3**	**173**

(4) Moreover, we expected to find a significant association between visual exploration measures and socio-cognitive impairments/ negative symptom severity.

2. Material & method

2.1. Participants

Fifty-eight individuals with 22q11DS aged between 6 to 27 years were included in this study (mean age= 15.7 ± 4.8 (50%) females). The presence of a 22q11.2 microdeletion was confirmed in all participants using quantitative fluorescent polymerase chain reaction (QF-PCR). Some patients met formal diagnostic criteria for a psychiatric disorder at the time of testing based on structured clinical interviews (see Table 1). Global intellectual functioning was measured using age-appropriate Wechsler scales (WISC (Weschsler, 1991, 2005) or WAIS (Weschsler, 1997, 2008)).

Seventy-nine healthy participants matched for age and gender distribution were also included and screened for the presence of any neurological problems, psychological, or learning difficulties. Participants were recruited through parent associations or word of mouth and were tested in our research laboratory in the context of an ongoing longitudinal study. Written informed consent was obtained from participants and/or their parents under protocols approved by the cantonal ethics commission of research.

Longitudinal data (ranging from two to three time points per participants) were available for a subsample of participants (20,23%) (See Table 2). In total, 173 testing points were acquired, 74 for 22q11DS individuals and 99 for healthy controls. For individuals with at least two time points available, the mean interval between two visits was 5.08 years (SD= 2.16). For participants with only one time point (79,76%), 40 (23%) of them did not return for a follow-up assessment. Fifty-one additional time points were available but were excluded from the current study because they did not fit the required criteria (see section inclusion criteria below). Prior to conducting analyses on trajectories of visual exploration we compared subjects who had longitudinal visits (n = 14) to the subjects that had only one visit (n=44). These two groups were not significantly different concerning age (p=0.850), full-scale IQ (p=0.940), and proximity index (p=0.781).

2.2. Eye-tracking measures

2.2.1. Stimuli

Three social scenes extracted from black and white French movies were presented to participants. The first and third scenes were extracted from *Le Deuxième Souffle* (Melville, 1966) whereas the second was extracted from: *Les Liaisons dangereuses* (Vadim, 1960). The scenes presented to participants lasted 75 seconds (2280 frames), 32 seconds (980 frames) and 102 seconds (3050 frames), respectively. These scenes were selected based on the number of characters involved to reflect varying levels of broadly defined social complexity. The first 'One-person scene', was selected due to its simplicity, as it concerns a context devoid of social exchange. This scene involves a single character having dinner at midnight. Suddenly, the clock rings and the man stands up to turn it off and then rips off the calendar sheet. The two additional scenes were selected to measure gaze behavior during dynamic social exchanges. The second scene involves a dyadic exchange: two main characters are sitting having a dynamic conversation about a future journey ('Dyadic interaction scene'). The third scene involves a triadic dialog ('Triadic interaction scene'), involving an older man sitting at a table on the right, a woman standing in the middle, and a man leaning against the table on the left. This scene presents three characters discussing the potential implication of one of the characters in a car-jacking heist.

After viewing the scenes, participants were asked to respond to a couple of questions regarding the scenes. For each scene, participants answered five questions related to the scene content with one correct proposition (1-point) and false propositions (0-point). An understanding score varying between 0 (poor understanding of the scene) and 5 (good understanding of the scene) was then computed (See supplementary material for detailed questions).

2.2.2. Tools and software

The data included in the present study were acquired in the context of a larger longitudinal study starting in 2002 and involved different eye-tracking devices; we thus combined data from three eye-tracking devices in order to increase the statistical power of our study.

One hundred twenty-seven time points were collected using the Tobii 1750 Eye-tracking device. Data capture was fixed at a 50 Hz sampling rate. The device contains a head-motion compensation enabling recordings without a head restraint device. One hundred twenty-three time points were presented on a screen with the following dimensions: 1024 × 768, whereas four participants were presented the scenes on an enlarged screen (1920 × 1200). The Clearview 2.6.3 eye-tracking software was used to both administer the eye-tracking tasks as well as to collect and export the eye gaze data.

Forty-six time points were collected using the T60XL eye-tracker device with a 17-inch display with a maximum resolution of 1920 × 1200 pixels and a sampling rate of 60 Hz. The Tobii studio software (www.tobii.com) was used to administer and export the eye gaze data. The size of the stimuli was kept constant over all three different setups, so all eye tracking metrics are obtained with the reference to the stimuli size, thus accounting for the difference in screen size. All the gaze landings were normalized to refer to stimulus space (and not the recording screen space), thus making them independent of the screen resolution. Downsampling gaze data obtained the independence of the sampling rate to match the stimuli frame rate (29.97 frames per second).

2.2.3. Inclusion criteria

Before inclusion in the study, a screening interview was conducted by phone to verify that participants met inclusion and exclusion criteria. Specifically, exclusion criteria for the control group were: 1) being born preterm, 2) current neurodevelopmental or psychiatric disorder (note that a past history of transient psychological difficulties not requiring the use of psychotropic medication or psychiatric hospitalization was not considered as an exclusion criterion), 3) present or past history of neurologic problems (e.g. epilepsy).

Participants who spent at least 70 % looking on the screen for each scene were included in the study, which constitute a stringent criteria to ensure the quality of the collected data. For this reason, 51 time points (32 patients and 19 controls) were not included in the current sample (See Table 1). A total of 173 testing points, including 74 time points for individuals with 22q11DS and 99 for healthy controls, was thus included in this study, as described in the participants' section.

Healthy participants were divided into four age bins in order to create different age-adapted norms (see) as follows: from 6 to 12 years old, 12 to 15 years old, 15 to 19 years old and 19 to 26 years old (See table S1 for a descriptive characterization of the subgroups). Healthy controls and 22q11DS individuals were matched for age and gender for each age bin. For individuals having more than one time point per defined age bin, only the more recent time point was kept for the analysis (N=22). To ensure that visual correction was appropriate,

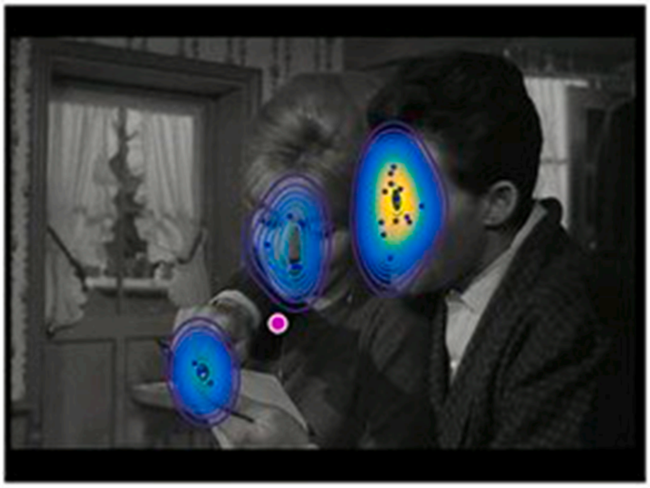

Fig. 1. Example of a normative map for one frame of the social scene (each small blue dot represents one control participant from the normative group; the lines represent the extent of the norm based on the kernel density algorithm. The purple circle represents the gaze fixation from a participant with 22q11DS on this specific frame).

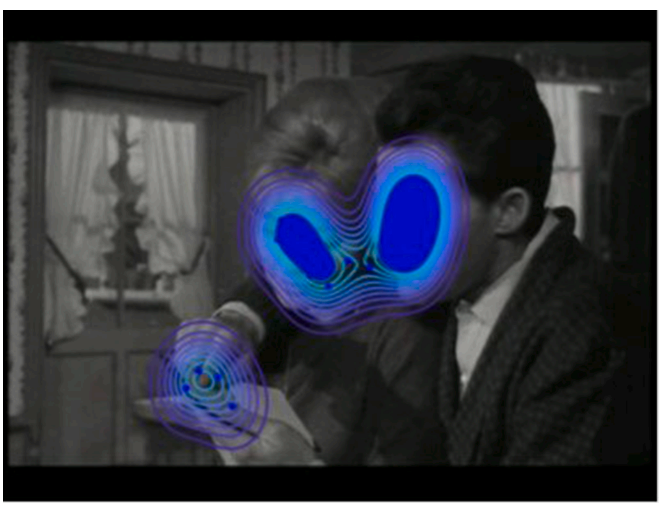

Fig. 2. Example of surface median contour for one frame of the social scene. The lines represent the extent of the norm based on the kernel density algorithm. The blue area represents the medium contour surface from one of the norms (6–12 years old) on this specific frame.

participants were instructed to bring and wear their glasses during the eye-tracking examination.

2.2.4. Eye-gaze parameters

We used a custom-developed data-driven method (Kojovic et al., 2020) that defines "normative" visual exploration behavior using gaze data from a given group without an a priori hypothesis. This method employs kernel density distribution estimation (Botev et al., 2010) on gaze coordinates in a frame-by-frame approach, thus yielding gaze density maps. We applied this method to gaze data from our control group in order to obtain a "norm" of visual exploration framewise. We then compared the gaze data of our patients to these normative density maps. Thus, we calculated the distance of each patient's gaze data from the norm. These obtained measures of the *Proximity from the norm* had values ranging from 0 to 1 (higher values indicate that the gaze was allocated closer to one of the foci of the normative group on a given frame).

Furthermore, we wanted to understand the developmental change of the visual exploration of this complex social scene for both groups and the potential difference between these pathways. For this, in each of the aforementioned age bins, we created normative gaze density maps. Across four age bins, gaze data from healthy controls were pooled together to define the norms. The same was done in our 22q11DS age bins by pooling together gaze data to obtain normative distributions for this group. Then, we compared the relative gaze dispersion between groups across the four age bins (See Fig. 1). The dispersion was calculated as the Surface of the median contour plotted over density estimation function (see Fig. 2). The greater values of *Surface of the median contour* measure indicated a more dispersed group gaze pattern (the group focus on the given frame covered a larger visual area). This measure of dispersion was available on a frame-by-frame basis for each group. Additionally, we also measured the number of separate attentional foci et a median level of the gaze distribution (Fig. 2).

2.3. Clinical assessment

2.3.1. Positive and negative symptoms

The severity of positive and negative symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS, (Kay et al., 1987)). The PANSS includes 30 items divided into three dimensions: positive, negative and general psychopathology. The total score of positive and negative symptoms were used for the analyses.

2.3.2. Anxiety

Anxiety level was assessed using the French revised Children's Manifest Anxiety Scale (RCMAS) in participants aged between 6–19 years (Reynolds, 1999). Data were available for 64 time points in the 22q11DS group and 68 time points in the control group. The RCMAS is a self-reported questionnaire composed of 37 items. Participants respond to each question by 'Yes' or 'No' scored respectively in '1′ or '0′. The RCMAS is composed of a total anxiety score and four separate subscales, including physiological anxiety, worry/over-sensitivity, social concerns/concentration and the lie scale. Higher scores indicate greater levels of anxiety. The total anxiety score was used as a global measure of anxiety.

2.4. Socio-cognitive measures

2.4.1. Emotion recognition

Emotion recognition was evaluated using a computerized multiple-choice exercise. Neutral faces and four universal emotions (happiness, fear, anger, and sadness) were selected and taken from a standardized set of photos (Ekman & Friesen, 1976). The total number of correct answers was used as the main measure.

2.4.2. Face recognition

The Benton Facial Recognition Test (BFRT; (Benton et al., 1994)) was used as a measure of face recognition ability. Data were available for 61 time points in the 22q11DS group and 96 time points in the control group. Participants were asked to match non-emotional unfamiliar faces. One target and six other black and white faces (male or female) were presented. First, participants were asked to match the target face with an identical photo. Secondly, they had to match the target face with three photos taken from different angles or different lighting conditions. The total number of correct answers was used as the main measure.

2.5. Statistical analyses

First, we aimed to examine the developmental trajectories of visual exploration of social information depending on the level of social complexity in individuals with 22q11DS. To do so, we compared the developmental trajectory of the scenes using mixed model regression analyses, as described in previous studies conducted by our group (see

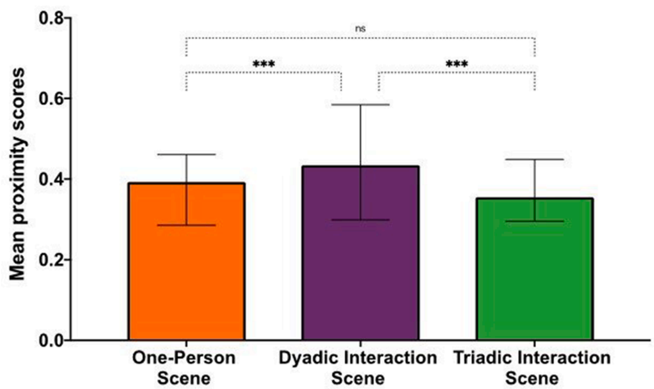

Fig. 3. Visual exploration in the 22q11DS population by scene (mean proximity scores).

(Maeder et al., 2016), as an example). This technique allows modeling the within-subject factor as a nested variable (Dedrick et al., 2009). For each scene, different models (constant, linear, quadratic or cubic) were fitted using the *nlmefit* function in MATLAB R2016b (MathWorks). Gender, IQ and the number of frames were entered as covariates. A Bayesian information criterion (BIC)-based model selection method was employed, as the BIC-based methods represent one of the most powerful model selection methods for the mixed model (Peng & Lu, 2012). Then a likelihood ratio test was conducted to compare statistical differences in trajectories depending on the level of social complexity. Two different measures are then obtained, allowing the examination of shape differences (interaction effect) or intercept differences (group effect) between the two groups. Please note that mixed-model regression analyses were corrected for false discovery rate. Non-parametric t-tests were conducted in order to compare the differences in terms of dispersion and number of foci between groups, as well as to discern the developmental patterns within each group across the four age bins. To better identify differences across age groups; the effect size was computed for each age bin comparison using the following formula: $r=Z/\sqrt{(N*2)}$, with Z corresponding to the Z value of the non-parametric *t*-test and N to the number of frames of the scenes (Rosenthal, 1984.)

Then, we tested the effect of potential confounds. To this end, we computed an overall index of proximity by averaging mean proximity scores from the three scenes for the rest of the analyses. First, to ensure that the differences were not related to intellectual impairment, we divided participants with 22q11DS into two groups according to the full-scale IQ scores ("lower than 70″ (N= 31) versus "higher than 70″ (N= 43) groups). We conducted the same analyses comparing the "higher than 70″ group to the "lower than 70 group".

Secondly, we compared the understanding scores for each scene between individuals with 22q11DS and healthy controls using ANOVAs. We then conducted the same mixed model analyses by adding the understanding scores as a covariate to control for its potential effect. We also examined whether understanding scores were related to the mean proximity value per scene in the 22q11DS population using correlation analyses. Finally, we tested whether having an attentional/hyperactivity deficit disorder (ADHD) could be related to the observed differences. Indeed, the ability to focus on relevant target stimuli against irrelevant stimuli relies on selective attention processes (Ungerleider & G, 2000). Participants with an ADHD diagnosis may thus fail to attend to appropriate social cues. Information was available for participants with 22q11DS below 18 years (N= 52 time points) for which a DICA has been conducted. We divided participants with 22q11DS with (N=18) and without (N=33) a formal ADHD diagnosis and then compared them using the mixed model analyses.

Finally, in the 22q11DS group we investigated the relationship between gaze behavior patterns with the severity of negative/positive symptomatology and socio-cognitive measures by conducting hierarchical stepwise regression analyses using the PANSS scores (negative or positive) or socio-cognitive measures as the dependent variable and the mean proximity scores as independent variables.

Table 3
Differences in longitudinal trajectories of visual exploration between scenes varying in terms of social complexity in participants with 22q11DS.

	Model fitted	Group p value	Interation p value
One-person/Dyadic/Triadic interaction scene	Linear	<0.001	<0.001
One-person vs. Dyadic interaction scene	Linear	<0.001	0.0001
One-person vs. Triadic interaction scene	Linear	0.0075	0.002
Dyadic vs. Triadic interaction scene	Linear	<0.001	<0.001

Significant values after multiple comparison corrections with false discovery rate (fdr). n.a. not applicable

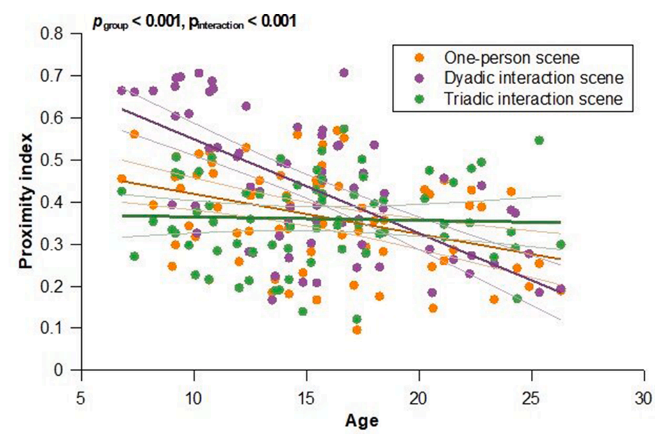

Fig. 4. Comparison of the developmental trajectories of visual exploration of social information depending on the social complexity (Orange: one-person scene, purple: dyadic scene, green: Triadic scene). Data points for a single subject are connected by a dotted line. Solid lines show the model fitted.

3. Results

3.1. *Visual exploration of social scenes of individuals with 22q11DS*

First, we assessed whether individuals with 22q11DS exhibited difference in visual exploration when looking at scenes of varying social complexity, by examining mean proximity values for each scene. We observed that individuals with 22q11DS highly variable mean proximity values, with values ranging between 0.14 (important divergence from normative gazing pattern) and 0.71 (strong coherence with normative gazing patterns) (See Fig. 3). While mean proximity for dyadic scene significantly differed from one-person and Triadic scenes (paired *t*-test <0.001), mean proximity between one-person and triadic scenes didn't differ (paired *t*-test= 0.38) (Fig. 3). The same pattern of results was found when screen attendance was used as a covariate to account for a potential effect of general interest on the Proximity index values. The mean proximity index for the dyadic scene significantly differed from the one-person and triadic scenes (paired *t*-test <0.001), while the mean proximity between the one-person and triadic scenes didn't differ (paired *t*-test= 0.18).

3.2. *Developmental trajectories of social perception in 22q11DS individuals*

We compared the developmental trajectories of visual exploration of

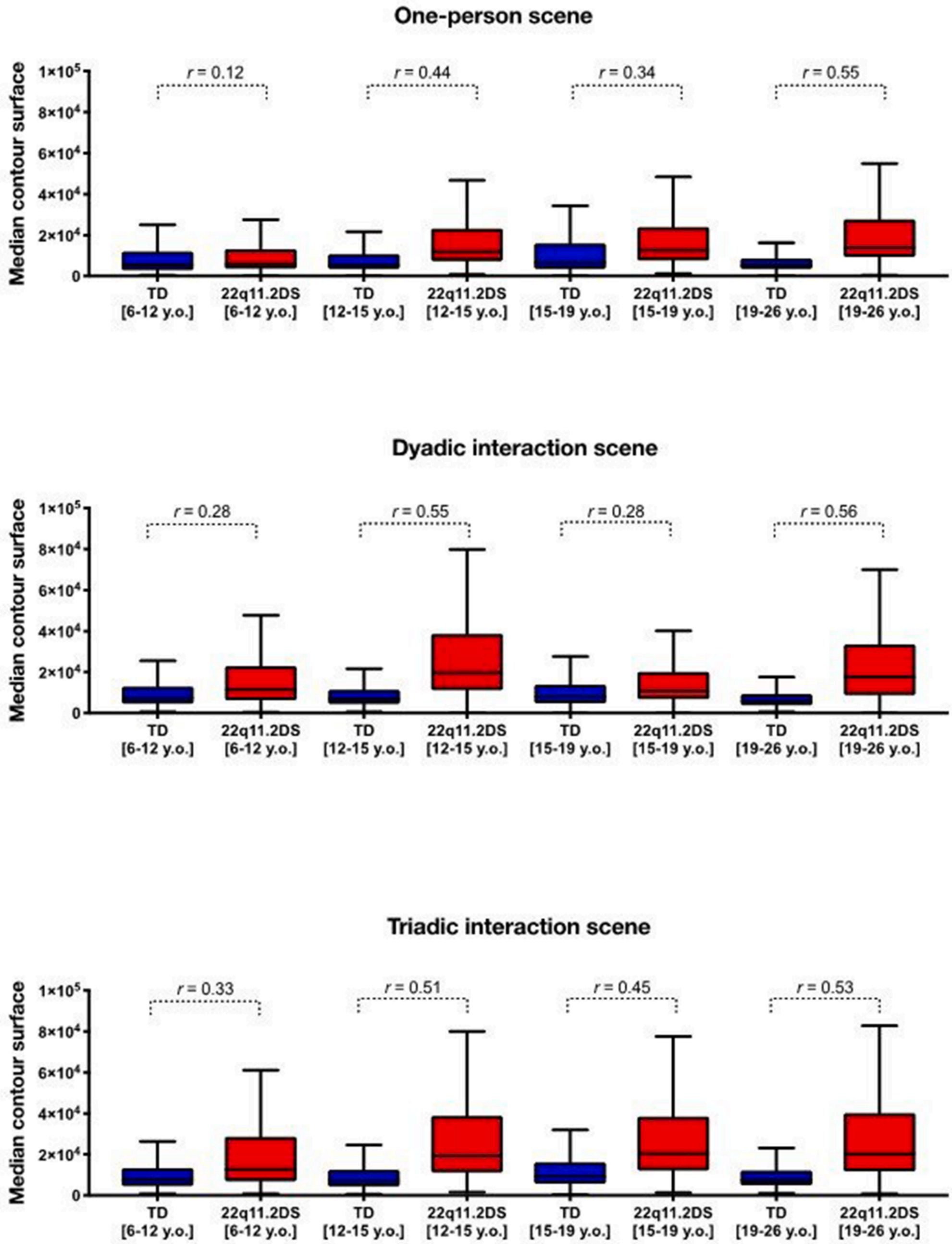

Fig. 5. Comparison of the dispersion (expressed as Median Contour Surface) between individuals with 22q11DS and healthy controls across group age per scene. *r*, effect size, y.o., years old.

three social scenes varying in terms of social complexity in individuals with 22q11DS. A linear model of change with age was fitted for the three scenes (Fig. 1 & Table 3). Regardless of the social complexity, gaze exploration in the 22q11DS population appeared to be more deviant from healthy individuals with age. Moreover, results revealed that visual exploration of social information tended to be more atypical depending on the social complexity ($p<0.001$) (See Fig. 4). Pairwise comparisons revealed that developmental trajectories of social exploration between the one-person and triadic scenes differ in terms of group and intercept. Significant differences in terms of both group and intercept were observed between the dyadic and the one-person/triadic scenes (See Fig. S1). Whereas developmental trajectories of social exploration appear constants with age for the Triadic scene, for the one-person and dyadic scenes with, gaze exploration was less atypical during early childhood and then tended to become increasingly atypical over time. This phenomenon was even more pronounced for the dyadic scene (See Fig. 4).

3.3. Dispersion between groups: cross-sectional analysis

22q11DS individuals exhibited higher median surface contour (dispersion) compared to healthy controls across all age group for each scene (all $p<0.001$). Effect size indicated that group difference in terms of inter-individual variability was more pronounced with age. This suggests that with increasing age, the visual exploration in HC becomes more focused (smaller area covered by the Median Contour Surface) while in 22q11DS patients we observed the opposite pattern: their gaze deployment became progressively more dispersed covering wide areas of the scene. (See Figs. 5 and 6).

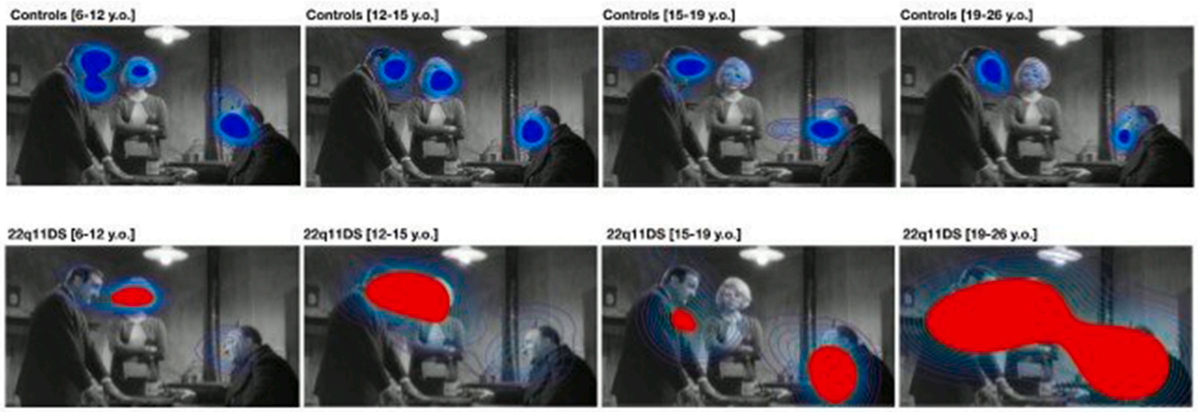

Fig. 6. Characterization of the evolution of visual exploration patterns in healthy controls (HC) and 22q22DS patients across 4 age bins. The dispersion is depicted using the Median Contour Surface (blue: HC, red:22q11DS).

3.4. Number of foci between groups: cross-sectional analyses

Overall, individuals with 22q11DS had a lower number of foci compared to healthy controls across all age groups (all $p<0.001$, See Fig. 7).

3.5. Effect of potential confounds

To better understand the differences in terms of social perception trajectories, the role of several factors including the full-scale IQ, the understanding of the scenes as well as attentional difficulties were examined. However, none of these factors were associated with the main variables of interest(See supplementary material).

3.6. Association between mean proximity and clinical measures

Hierarchical regression analysis controlling for full-scale IQ revealed that global mean proximity score was significantly associated with the severity of negative symptoms as well as the degree of anxiety in 22q11DS individuals. No significant association was found with positive symptoms (See Table 4).

3.7. Association between mean proximity and socio-cognitive measures

Hierarchical multiple regressions controlling for full-scale IQ were used to investigate the association between global mean proximity score and socio-cognitive measures. Global mean proximity scores were significantly associated with face recognition performance. No association with emotion recognition was found (See Table 5).

4. Discussion

In this study, we used a data-driven methodology to characterize visual exploration of complex social scenes compared to healthy controls and aimed to identify a specific time window for the onset of impaired social perception in 22q11DS. We examined associations of visual exploration measures with socio-cognitive and negative symptoms measures.

For each scene and regardless of the level of social complexity, participants with 22q11DS exhibited an atypical pattern of visual exploration. This deviant visual exploration compared to normative maps, suggests that individuals with 22q11DS were less efficient at detecting socially-relevant information compared to their typically developing peers. This result is in accordance with previous literature showing atypical face processing in 22q11DS, characterized by less scanning to the eyes and more attention to less informative facial features such as the mouth (Campbell et al., 2010; Glaser et al., 2010; Zaharia et al., 2018). Results also appear similar to those reported in individuals with schizophrenia, showing limited visual scanning of social information (M. J. Green et al., 2003; Loughland et al., 2002). Moreover, after controlling for potential confounds, neither intellectual disability, understanding issues, or attentional difficulties seemed to contribute to the atypical social processing observed in 22q11DS.

When examining the maturation of social perception over time, our findings suggest that divergence in visual exploration is present early in the development of 22q11DS children and thus precede the emergence of clinical manifestations. This is in agreementwith previous literature demonstrating atypical face processing since childhood in 22q11DS (Zaharia et al., 2018) and highlights the necessity to develop and implement early remediation programs to improve or prevent social exploration impairments in this population. Through our results, we demonstrated that visual exploration appears to be constant for social scenes of high complexity in 22q11DS individuals. This result suggests that the pattern of visual exploration is impaired since the first stage of life for social information with high complexity, while for scenes with low and intermediate complexity we observed that visual exploration becomes more atypical with age f.This last result seems indicate that social exploration is partially reversed for less complex social information during the first year of life and then tend to dramatically decreased up to 6 years old. There are several possible interpretations of these results. One explanation would be that individuals with 22q11DS might tend to avoid social information. Indeed, previous studies showed (1) an association between anxiety level and eye region avoidance in 22q11DS (Glaser et al., 2010), (2) a lower percentage of first and second fixations on the eyes' region when viewing face stimuli in 22q11DS compared to healthy controls (Zaharia et al., 2018). Thus, individuals with 22q11DS might consider social information as stressful and thus try to reduce the attendance, resulting in the observed atypical pattern of visual exploration. Another possible explanation is related to the social motivation theory (Chevallier et al., 2012), This model proposes that in conditions such as autism, reduced social interest decreases social inputs and opportunities to learn, which results in reduced abilities in social cognition. As children have increased difficulties understanding their social environment, they progressively further decrease social motivation over time. Based on this theory, one could hypothesize that social motivation impairments in 22q11DS might explain the linear decline of social perception with age.

To better understand how visual scanning strategies in individuals with 22q11DS differed from healthy controls, additional eye-tracking parameters were used: the median contour surface to assess gaze dispersion across groups and the number of foci reflecting how much individuals tend to focus their attention on similar elements of the

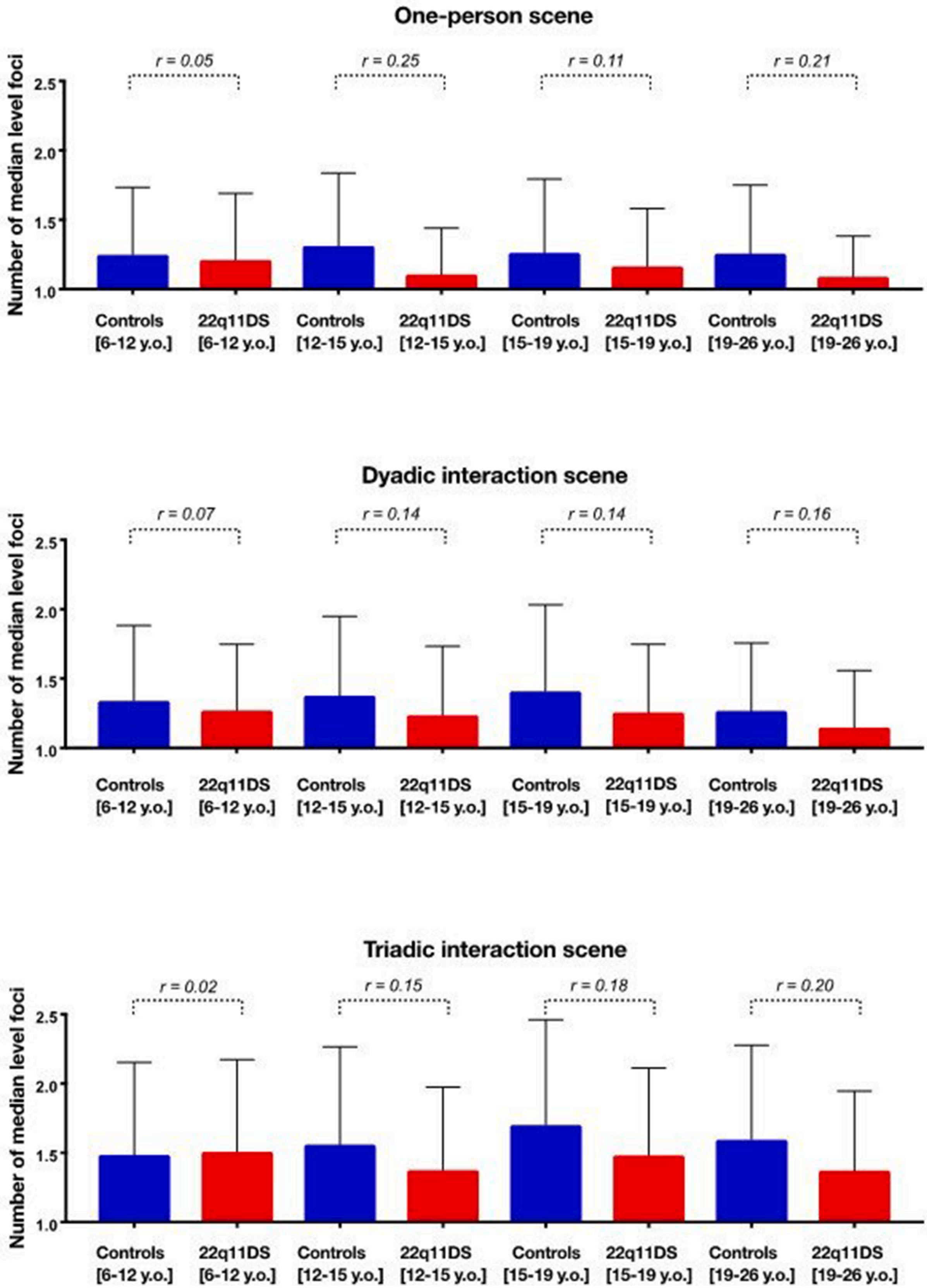

Fig. 7. Number of foci between 22q11DS individuals and healthy controls across age groups and complexity level. *r,* effect size, y.o., years old.

Table 4
Hierarchical regression models examining the association between mean proximity and clinical measures.

Steps	Dependent variables Independent variable	R^2	R^2 change	F	P
	PANSS negative				
Step 1	Full scale IQ	0.534	0.285	25.13	0.000
Step2	**Mean proximity**	**0.580**	**0.336**	**15.70**	**0.033**
	PANSS positive				
Step 1	Full scale IQ	0.467	0.218	17.58	0.000
Step2	Mean proximity	0.467	0.218	8.65	0.989
	Anxiety (RCMAS)				
Step 1	Full scale IQ	0.203	0.041	2.57	0.114
Step2	**Mean proximity**	**0.347**	**4.05**	**4.05**	**0.022**

* PANNS, Positive and Negative Syndrome Scale, RCMAS, Revisited Children's Manifest Anxiety Scale

Table 5
Hierarchical regression models examining the association between mean proximity and socio-cognitive measures.

Steps	Dependent variables Independent variable	R^2	R^2 change	F	P
	Emotion recognition				
Step 1	Full scale IQ	0.306	0.094	6.09	0.017
Step2	**Mean proximity**	0.309	0.096	0.054	0.708
	Face recognition				
Step 1	Full scale IQ	0.050	0.002	0.14	0.599
Step2	**Mean proximity**	**0.336**	**0.113**	**3.64**	**0.01**

scenes. First, we observed that individuals with 22q11DS had a more scattered gaze exploration compared to healthy controls for all age bins. Typical children around 4–5 years exhibit higher gaze dispersion compared to adults (Kowler & Martins, 1982). Afterwards, gaze dispersion tends to decrease and to be relatively similar to adults (Rider et al., 2018). It has been proposed that reduced gaze dispersion with age could be related to improvements in attentional processes and a better understanding of what is being viewed (Kirkorian et al., 2012). Higher gaze dispersion with age in 22q11DS could therefore be related to the presence of attentional impairments that is a common feature of the 22q11DS profile (Niarchou et al., 2015; Schneider et al., 2014). However, when comparing developmental trajectories between participants with and without a formal diagnosis of ADHD, no significant difference was found. Further studies examining gaze dispersion in the 22q11DS population are thus required. Regarding the number of foci, we found a reduction in the 22q11DS group compared to controls across all age bins. This result suggests lower exploration coherence within the 22q11DS group. It is possible that individuals with 22q11DS favor a more global (shallow) than a focal (in-depth) exploration strategy, focusing their attention on random features in a less sustained manner. This would explain the broader inter-individual spatial variability and the lack of consistency regarding the foci of interest among individuals with 22q11DS. However, difficulties in local rather than global processing have been reported in this population (Giersch et al., 2014). Additional studies examining potential deficits in global processing in 22q11DS should thus be conducted.

By examining associations between social perception and clinical measures, we found that abnormal visual exploration was significantly correlated with negative symptom severity and face recognition, whereas no association with emotion recognition was observed. These findings suggest that deviant social perception impacts socio-cognitive processes and particularly face recognition. Previous studies demonstrated an eye region avoidance and a bias toward the mouth in 22q11DS (Glaser et al., 2010; Zaharia et al., 2018). Whereas the eye region appears crucial for face recognition, other facial features and particularly the mouth, have been demonstrated as helpful for emotion recognition(Boucher & Ekman, 1975), which could explain the absence of association with emotion recognition. Moreover, our results strongly suggest that atypical social perception is associated with negative symptom severity in 22q11DS individuals. Because social perception impairments appear early in this population and notably before the emergence of negative symptoms, one could hypothesize that targeting visual exploration of social information early in life might prevent the emergence of negative symptoms. Visual exploration of social information could thus represent a key intervention target for negative symptoms in 22q11DS.

There are several limitations to this study. First, several patients were medicated at the time of the testing, but the impact of these medications could not be investigated in this study. Secondly, previous studies have highlighted a general visual processing deficit in 22q11DS (K. McCabe et al., 2011; K. L. McCabe et al., 2016), which could influence our results. Unfortunately, our protocol did not include a general visual processing task, which prevented us to from taking this into account. Another potential limitation concerns the high prevalence of eyelid hooding in this specific population (20 to 67%,(von Scheibler et al., 2022)) that might to some extent still impact the quality of the data used in this study, despite our very stringent eye-tracking based exclusion criteria. Additionally, participants were not instructed to remove contact lens during the eye-tracking evaluation to ensure that visual correction was applied. Previous literature has demonstrated that contact lens can decrease accuracy and precision of eye-tracking methods (Holmqvist et al., 2022), which could thus have impacted the quality of our data. Finally, one of the strengths of the manuscript lies in the inclusion of longitudinal data., there was a significant difference between the amount of data collected for the first two timepoints compared to the third timepoint, which might induce a risk of bias in our longitudinal analyses. Unfortunately, data for the third timepoint were not yet collected at the time of data analysis.

Our study highlighted atypical social exploration patterns in 22q11DS from childhood onwardsthat tends to increase over time. These findings provide a better characterization of the attendance to social information in this syndrome and bring crucial information regarding the onset of social perception impairments. This study also highlights the putative role of deviant social exploration in the development and maintenance of several clinical manifestations. Intervention programs targeting social exploration impairments should be considered in this population (e.g. (Choi et al., 2017).

Open practices

"The experiments reported in this article were not formally preregistered. Neither the data nor the materials have been made available on a permanent third-party archive; requests for the data or materials can be sent via email to Maude.Schneider@unige.ch".

Author contributions

SE, MSchn, LD and NK designed the study. MSchn contributed to the data collection. NK developed the methodology. LD and NK analyzed the data. LD wrote the first draft of the manuscript and NK the methodology part. All authors contributed to the interpretation of the results. All authors have approved the final manuscript.

Declaration of Competing Interest

The author(s) declared no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115074.

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