Social skills and associated psychopathology in children with chromosome 22q11.2 deletion syndrome: implications for interventions

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Abstract:

Background Although distinctive neuropsychological impairments have been delineated in children with chromosome 22q11 deletion syndrome (22q11DS), social skills and social cognition remain less well-characterised.

Objective To examine social skills and social cognition and their relationship with neuropsychological function/behaviour and psychiatric diagnoses in children with 22q11DS.

Methods Sixty-six children with 22q11DS and 54 control participants underwent neuropsychological testing and were administered the Diagnostic Analysis of Non-Verbal Accuracy (DANVA) for face and auditory emotion recognition, a measure of social cognition: their parents/guardians were administered the Social Skills Rating System (SSRS) – parent version, Child Behavior Checklist (CBCL) – parent version and the Computerised Diagnostic Interview Schedule for Children (C-DISC).

Results The 22q11DS group exhibited significantly lower social skills total score and more problem social behaviours, lower neurocognitive functioning, higher rates of anxiety disorders and more internalising symptoms than the control group. Participants with 22q11DS also exhibited significant deficits in their ability to read facial expressions compared with the control group, but performed no differently than the control participants in the processing of emotions by tone of voice. Within the 22q11DS group, higher social competency was correlated with higher global assessment of functioning and parental socio-economic status. Social competency was worse in those with anxiety disorders, attention deficit hyperactivity disorder, more than two

psychiatric diagnoses on the C-DISC and higher internalising symptoms. No significant correlations of SSRS scores were seen with IQ, executive functions, attention, or verbal learning and memory. No correlations were found between social cognition and social skill scores.
Conclusion Our results indicate that social skills in children with 22q11DS are associated with behaviour/emotional functioning and not with neurocognition. Thus, treating the behaviour or emotional problems such as attention deficit hyperactivity disorder and anxiety disorders may provide a pathway for improving social skills in these children.

Keywords: behavior | DiGeorge syndrome | emotional processing | neuropsychology | social cognition | velocardiofacial syndrome | psychology

Article:

Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS), also known as DiGeorge syndrome or velocardiofacial syndrome, is the most common chromosomal microdeletion in humans, occurring in 1 in 1600 to 1 in 2000 live births (Shprintzen 2008). The physical phenotype associated with 22q11DS is variable; the most common manifestations include conotruncal heart abnormalities, velopharyngeal insufficiency, hypoparathyroidism and immune deficiency (Shprintzen 2000, 2008). The neurocognitive impairments in individuals with 22q11DS have proven to be more consistent, with deficits occurring in 80–100% of affected individuals. The mean intelligence quotient (IQ) is reported to be 75 and almost 50% will have a diagnosis of intellectual disability (Swillen *et al*. 1997; Woodin *et al*. 2001). A complex array of deficits has been reported, with deficits in visual-spatial processing, executive function, attention, verbal learning, working memory, arithmetic and language, with relative strengths in selected reading and spelling skills (Golding-Kushner *et al*. 1985; Gerdes *et al*. 1999;Lewandowski *et al*. 2007; Simon *et al*. 2008). These impairments lead to poor school performance and more generally, to lower adaptive skills. Similarly, behavioural and emotional problems occur in approximately 50% of children with 22q11DS, including attention deficit hyperactivity disorder (ADHD) and anxiety disorders (Swillen *et al*. 1999, 2000).
Social skills in children with 22q11DS have not been as well characterised as other behavioural problems. Earlier descriptive reports included poor social competence, concrete thinking and difficulties generalising previous experiences to novel situations (Golding-Kushner *et al*. 1985; Furst *et al*. 1995). Although a few recent empirical studies have confirmed the presence of social skill/social behaviour impairments in children with 22q11DS (Woodin *et al*. 2001; Kiley-Brabeck & Sobin 2006; Jansen *et al*. 2007), others have reported no differences in the social

skills of children with 22q11DS. In one such study, children with 22q11DS were no different from an age-matched comparison group of individuals with developmental disabilities on social problems as measured by the Child Behavior Checklist (CBCL) (Feinstein *et al*. 2002). A second study of infants and toddlers with 22q11DS used maternal reported social adaptive milestones and these were described as being intact (Roizen *et al*. 2007). Because these studies did not use healthy control groups or utilised very young children with 22q11DS, the social skill impairments in the 22q11DS group may not have been as pronounced. Thus far, only two studies have examined the relationship between social competence and neuropsychological performance in children with 22q11DS (Kiley-Brabeck & Sobin 2006; Jansen *et al*. 2007). Kiley-Brabeck *et al*. (2006) found an association between poor social competence and poor executive function, whereas Jansen *et al*. (2007) did not find an association between poor social competence and IQ in their cohort of 22q11DS. We have reported previously that poor social competency correlates with lower socio-economic status (SES) in 22q11DS, which raised the possibility that social skills competence may be improved with interventions aimed at improving access to services and other resources (Shashi *et al*. 2010). Other correlates of the social skill problems in 22q11DS have not been examined.

Relatively little is known about the social functioning of children with 22q11DS in the context of the increased risk of psychiatric disorders in these individuals. Debbane *et al*. (2006) reported that social functioning in 22q11DS was worse in those with psychotic symptoms than in those who do not have psychotic symptoms, similar to the findings seen in studies of individuals at high risk of schizophrenia in the general population (Miller *et al*. 2002; Johnstone *et al*. 2005). This finding underscores the importance of social functioning as a correlate of psychosis, or perhaps psychiatric disturbances more broadly.

Social cognition, referred to as the mental operations underlying social behaviour, is a broad, multifaceted construct that refers to the cognitive and emotional functions required to understand and predict other people's mental states and behaviour; the term includes a diverse array of processes such as emotional processing, social knowledge, theory of mind and attributional style (Adolphs 2009). A few studies have examined face emotion recognition as an indicator of social cognition deficits in 22q11DS. In an fMRI study, Andersson *et al*. (2008) reported a lack of activation of typical face processing networks in adolescents with 22q11DS, with deficient activation of the fusiform gyrus in response to neutral faces and lack of activation of the superior temporal sulcus in response to fearful faces. Another study in adolescents with 22q11DS examined emotional face stimuli processing using visual scan path, and reported a visual scan path pattern that differed significantly from the controls; fewer fixations and shorter scan path length. The 22q11DS group was found to spend significantly less time in looking at the eye regions of faces and more time looking at the mouth region. They also demonstrated decreased

accuracy for recognition of fear and disgust relative to controls (Campbell *et al*. 2010). Similarly, Glaser *et al*. (2010) investigated eye-gaze during a face-processing task and reported that children with 22q11DS spent less time on the eyes. A reduction in eye-time during facial emotion recognition has been thought to be related to impaired emotional perception in children with autism as well as in typically developing individuals (Klin *et al*. 2002; Schyns *et al*. 2002). Interestingly, Glaser *et al*. (2010) reported that the time spent on the eyes was less in those with lower IQ and higher anxiety, providing preliminary evidence that neuropsychological functioning and psychopathology may modulate social cognition in children with 22q11DS. Individuals with 22q11DS demonstrate high rates of psychiatric illnesses, the most significant being schizophrenia-spectrum disorders, which occurs in 10–25% of affected individuals, beginning in late adolescence/early adulthood. Furthermore, 30% of adults go on to have a diagnosis of schizophrenia (Shprintzen *et al*. 1992; Pulver *et al*. 1994; Papolos *et al*. 1996; Murphy *et al*. 1999) and social cognition in the form of theory of mind is worse in those with psychosis than in 22q11DS patients who do not have psychosis (Chow *et al*. 2006). Research studies have documented impairments in social cognition in patients with schizophrenia in the general population, frequently in theory of mind, emotional perception and knowledge, and social perception and knowledge. In this regard it is thought that social cognition may be more predictive of poor functional outcome than neurocognition in schizophrenia (Fett *et al*. 2011; Mancuso *et al*. 2011). Poor functionality is common in children with 22q11DS, even before the occurrence of psychoses, adding to the decreased quality of life as well as increased parental stress (Kobrynski & Sullivan 2007; Hercher & Bruenner 2008). These factors indicate the potential importance of understanding the social cognitive deficits as a first step towards improving these deficits in children with 22q11DS and increasing overall functionality. We undertook an investigation to examine social skills and social cognition (emotion recognition) in children with 22q11DS, and to examine the associations between neuropsychological functions, psychopathology, social skills and social cognition in these children. Our hypotheses were that: (1) children with 22q11DS would have significantly lower social competence and social cognition compared with control participants; and (2) poor social skills in children with 22q11DS would correlate with neuropsychological functions, social cognition and psychopathology, specifically attention problems, anxiety disorders and the presence of multiple psychiatric diagnoses as well as the SES of the family. Figure 1 shows a conceptual model of the predicted relations between the different domains that we measured. To our knowledge, this is the first study to examine the interrelationships of social skills, social cognition and other neuropsychological findings in children with 22q11DS.

Figure 1. Path diagram representing hypothesised relationships between Social Skill, Social Cognition, Neuropsychological Functions, Psychiatric Diagnoses and SES, in children with 22q11DS.

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Methods

The study was approved by the Institutional Review Boards of Duke University Medical Center and Wake Forest University Health Sciences. Informed consent was obtained from the parent/guardian of the children who participated in the study.

Participants

Participants included 66 subjects with 22q11DS and 54 controls. The 22q11DS participants were enrolled through the genetics clinics at Duke Medical Center and Wake Forest University. The control participants were age (within 9 months) and gender-matched to the participants with 22q11DS and were recruited through the local paediatric practices and public school systems. SES was ascertained from all participants by using the Hollingshead and Redlich scale (Hollingshead 1975; Hollingshead & Redlich 2007). Children (22q11DS and controls) with a history of psychosis, bipolar illness or major depression were excluded from the study, as these participants are part of a longitudinal study assessing risk factors for psychosis in 22q11DS. Our cohort of 66 subjects with 22q11DS was representative of the population of children with this disorder, as the vast majority was recruited from the genetics clinic, where overall care is provided to these children and not from any subspecialty clinic. The 22q11DS and control groups did not differ on sex composition (52% male and 54% male respectively, $P = 0.81$), age (10.5 ± 2.6 years and 11.0 ± 2.3 years respectively, $P = 0.24$) and overall SES ($P = 0.26$). However, differences were found in ethnic composition between the groups (subjects: 83% Caucasians, 6% African-Americans, 6% Hispanic, 3% biracial and 2% Native American; controls: 69% Caucasians, 26% African-Americans, 3% Hispanic and 2% biracial; $P = 0.03$). Because the correlations between social skills, social cognition and other measures were performed only within the 22q11DS group, and not across the 22q11DS and control groups, we did not include race as a covariate in the analyses.

Measures of cognitive functioning

All the assessments were administered by trained graduate students in Psychology or a doctoral level clinician. The participants underwent a battery of tests, based on the NIMH-MATRICS for

assessment of neurocognition in schizophrenia (Kern *et al*. 2004), designed to measure verbal and non-verbal abilities (WISC-IV) (Wechsler 2003), sustained attention (CPT_AX and CPT_IP) (Cornblatt*et al*. 1988), executive functions (Wisconsin Card Sorting Test, WCST) (Chelune & Baer 1986), verbal learning and memory (California Verbal Learning Test-Children's Version, CVLT) (Delis *et al*. 1993).

Measures of psychopathology and behaviour

The CBCL (Achenbach & Ruffle 2000) and the C-DISC (NIMH-CDISC 2004) were administered to the parents/guardians of the children with 22q11DS and the control participants; both instruments are well-validated with high rates of reliability. The CBCL provided internalising, externalising and total problems symptoms scores for assessment of behaviour. The CBCL is a widely used parent-rating scale for child social-behavioural problems and is highly reliable (test–retest reliability: $r = 0.95$; inter-interviewer reliability: $r = 0.93$) (Achenbach & Ruffle 2000). We did not utilise the social skills T-score and social problems T-score from the CBCL, because we had clinical scales to assess social competency and social problems, in the form of the SSRS.

The C-DISC is a comprehensive, structured interview that covers 36 mental health disorders for children and adolescents using DSM-IV criteria (NIMH-CDISC 2004). The C-DISC is the most widely used and studied mental health interview that has been tested in both clinical and community populations. From the C-DISC, we extracted thespecific diagnoses, the presence of two or more diagnoses and whether a child received a diagnosis of any anxiety disorder. A global assessment of function (GAF) score was computed by the clinicians assessing the children. The GAF is a numeric scale (0–100) that is used by clinicians to rate functionality of individuals based on the social, occupational and psychological functioning using DSM-IV criteria (Hall 1995).

Social skills

Social skills of the participants were measured using the parent rated SSRS that measures social behaviours and behaviours that could interfere with the development of social skills and academic functioning (Gresham & Elliot 1990). The scale was designed to screen and classify social skills of children in the pre-school through high school grades. It yields standardised total social skills scaled score, and four nominal behaviour ratings. The measures used in our study were the norm-based total score and problem behaviours scale.

Social cognition

The emotion perception and processing domain of social cognition was tested using the Diagnostic Analysis of Non-Verbal Accuracy (DANVA), Child Facial Expressions and the Child Paralanguage subtests (Nowicki & Duke 1994). The computer-administered facial expression

subtest included 24 photographs of child models (12 female, 12 male per subtest) displaying equal numbers of high- and low-intensity expressions of happiness, sadness, anger and fear. Faces appeared for 2 s. The computer-administered paralanguage subtest includes 16 trials in which a 10-year-old girl repeated the sentence 'I am going out of the room now, but I'll be back later' in such a way as to communicate happy, sad, angry and fearful emotion. In a forced-choice format, participants indicate the emotions expressed by the face/tone of voice by a button-press. Results were measured in terms of total errors (i.e. misidentified emotions) and number of high- and low-intensity errors. The DANVA has been shown to be reliable and valid (Nowicki & Carton 1993; Nowicki & Duke 1994).

Data analyses

Statistical tests were performed using SPSS version 18.0, with independent sample *t*-tests for continuous variables. Fisher's exact test was employed for 2 × 2 contingency tables and chi-square for other categorical variables to examine the differences in social skills, social cognition, psychopathology and neuropsychological functions between the two groups. Pearson correlations were computed to determine associations between the social skills, social cognition and neuropsychological/behaviour/psychiatric measures. In order to examine if social skills scores were predicted by ADHD or any anxiety disorder and if the association was different in the 22q11DS and control groups (i.e. whether group membership moderated the relations of social skills deficits), a series of linear regression analyses were computed. Group (22q11DS and control group) was entered at the first step, the dichotomous code for the disorder (any anxiety/ADHD) was entered at the second step and group by disorder interaction was entered in the final step. A significant interaction term would indicate that the group moderated the relation of social skills deficits and the disorder. Similarly, we examined the variance associated with social skills competence and problem behaviours in functionality (GAF), using linear regression analyses.

Results

Social skills

Children with 22q11DS exhibited significantly lower social skills total score and more problem behaviours than the control participants, with moderate effect sizes being present (Table 1).

Table 1. Cognitive, behaviour problems, social skills and psychopathology in children with 22q11DS compared with controls

Measures	22q11DS Mean (SD)	Control Mean (SD)	*t*-value	Cohen's d

Continuous performance test – AX	1.35 (1.14)	2.65 (1.05)	−6.37***	**>1**
Continuous performance test – IP	0.38 (0.47)	1.09 (0.64)	−6.95***	**>1**
WISC – Verbal comprehension	77.67 (12.77)	98.11 (12.34)	−8.75***	**>1**
WISC – Perceptual organisation	74.83 (12.28)	101.38 (14.04)	−10.95***	**>1**
WISC – Working memory	78.61 (15.00)	97.48 (10.16)	−7.71***	**>1**
WISC – Processing speed	77.60 (13.82)	95.19 (13.59)	−6.84***	**>1**
WCST – Perseverative errors	86.98 (11.05)	103.63 (14.17)	−7.10***	**>1**
California Verbal Learning Test score	38.66 (11.61)	48.44 (10.31)	−4.81***	**0.89**
CBCL – Internalising score†	59.81 (13.04)	49.98 (12.91)	4.10***	**0.75**
CBCL – Externalising†	52.86 (9.19)	49.31 (11.26)	1.88	0.34
CBCL – Total Problem Score†	61.16 (9.75)	50.44 (12.17)	5.30	**0.97**
SSRS – Total score	89.62 (17.67)	100.17 (16.28)	−3.34***	**0.60**
SSRS – Problem behaviours score	105.34 (15.24)	98.07 (14.45)	2.65**	**0.50**
Any anxiety disorder	45.4%	15.7%	FET < 0.001	
ADHD	39.3%	28.8%	FET NS	
GAF	63.59 (8.46)	70.79 (10.29)	−4.07***	**0.76**

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$. Medium and large effect sizes are in bold.

† CBCL data available for 63 participants with 22q11DS and 55 control participants.

Note: Scores for the GAF are reported in raw scored, with higher scores reflecting a more intact performance; CBCL scores are reported in T-score format with a mean = 50 ± 10, with higher scores reflecting more impairment; CPT and CVLT scores are reported in z-scores, with mean = 0 ± 1, with higher scores reflecting a more intact performance; WISC and WCST scores are reported in standard scores with a mean = 100 ± 15, with higher scores reflecting better performance; SSRS scores are reported in standard scores also.

FET, Fisher's exact test; NS, not significant.

Neuropsychological functions and psychiatric diagnoses

The 22q11DS and control groups differed significantly in neuropsychological functioning and the rate of internalising symptoms (Table 1). The rate of anxiety disorders was also significantly different, with 45% of the participants with 22q11DS having anxiety disorders compared with

16% of the control participants ($P < 0.001$). A portion of these data have been previously published (Lewandowski *et al*. 2007). There was no difference in the incidence of ADHD between the two groups, because typical children with ADHD were allowed to participate in the study; however, the rate of ADHD in the 22q11DS group of 39%, is much higher than in the general population (Barbaresi *et al*. 2002). GAF was significantly lower in the 22q11DS group..

Social cognition/emotional perception and processing

Data on the DANVA measures were available only for 18 subjects and 17 controls; there were no differences between 22q11DS and control participants in age and gender. Significant differences were found between the two groups in emotional perception and processing testing on the facial expressions subtest; however, no significant differences were found in the emotional perception and processing by paralanguage subtest between the two groups (Table 2). Thus, children with 22q11DS exhibited significant deficits in emotional perception in their ability to read facial expressions, but performed relatively better in the processing of emotions by tone of the voice.

Table 2. Social cognition measures in 22q11DS and control groups tested using Diagnostic Analysis of Non-Verbal Accuracy-form 2 (DANVA-2)

Measure [†]	22q11DS Mean (SD)	Control Mean (SD)	*t*-value	Cohen's d
Facial expressions				
Number of total errors	5.72 (3.03)	2.44 (1.32)	4.01***	**>1.00**
Number of high-intensity errors	1.61 (1.79)	0.44 (0.63)	2.49**	**0.87**
Number of low-intensity errors	4.11 (1.71)	2.00 (1.03)	4.29***	**>1.00**
Z-score	−0.89 (1.19)	0.37 (0.52)	−3.91***	**>1.00**
Paralanguage				
Number of total errors	6.88 (3.77)	5.06 (1.84)	1.74	**0.61**
Number of high-intensity errors	2.35 (1.9)	1.75 (0.86)	1.16	**0.40**
Number of low-intensity errors	4.53 (2.4)	3.31 (1.45)	1.75	**0.60**

Z-score	−0.5 (1.09)	0.019 (0.5)	−1.74	**0.64**

** $P < 0.05$, *** $P < 0.001$. Medium and large effect sizes are in bold.

† Data available for only 18 22q11DS subjects and 17 controls.

Correlation between neuropsychological functions and social skills

We examined the correlation between the neuropsychological measures and social skills in children with 22q11DS. Although all of our analyses were based on *a priori* hypotheses, we applied the Bonferroni correction method for multiple correlations (Table 3).

Table 3. Pearson partial correlations of social skills with measures of neuropsychological functions and socio-economic status in children with 22q11DS

Measures	SSRS – Total score	SSRS – Problem behaviours score
GAF	**0.42** ***	−0.33**
DISC – Any anxiety disorder	**−0.40*** **	0.38**
DISC – ADHD	−0.33**	0.27*
More than 2 diagnosis on C-DISC	**−0.41*** **	0.32**
CBCL – Internalising score	**−0.40*** **	**0.49*** **
Continuous performance test – AX	−0.14	0.11
Continuous performance test – IP	−0.06	0.02
WISC – Verbal comprehension	0.08	0.04
WISC – Perceptual organization	0.12	−0.08
WISC – Working memory	0.14	−0.14
WISC – Processing speed	0.011	−0.07
Wisconsin Cart Sort Perseverative errors	−0.13	0.25
California Verbal Learning Test	−0.17	0.22
Overall SES	−0.32**	0.07
DANVA – total errors on visual subtest	0.054	−0.03
DANVA – total errors on paralanguage subtest	0.202	−0.054

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$.
Magnitude of correlation: 0.1 = small, 0.3 = moderate and ≥0.5 = large; adjusted level of significance of correlation coefficients after Bonferroni's correction is 0.003; correlations that survive Bonferroni corrections are bolded.

Social Competence Correlations: Lower social competency, based on the SSRS total score was associated with higher rates of anxiety disorders, ADHD, having more than two psychiatric diagnoses and more internalising symptoms. Social competency was positively associated with GAF as well as parental SES (note that a lower SES is indicated by a higher number). Lowering the α to 0.0036 (0.05/14 comparisons) with the application of the Bonferroni corrections resulted in the associations between social skills competence and anxiety disorders, internalising symptoms and GAF to remain significant, as seen in Table 3. There were no significant correlations of SSRS total scores with IQ indices, executive function, attention, and verbal learning and memory.
Social Problem Behavior Correlations: Problem behaviours on the SSRS were significantly more in those with more internalising problems, even after application of the Bonferroni correction. Those with anxiety disorders, ADHD, more than two psychiatric diagnoses, and lower GAF had more problem behaviours, but these associations did not survive Bonferroni corrections (Table 3). Problem behaviours on the SSRS did not correlate with neurocognitive functioning.

Correlations of emotion recognition with neuropsychological function and social skills

The correlations between the neuropsychological data and the DANVA scores on facial expression recognition, as well as the social skills scores and facial expression recognition were examined in the 22q11DS group and no significant correlations were found.

Regression analyses

On linear regression analyses (Tables 4–6), we found that both anxiety disorders and ADHD accounted for significant variance in social skills total score and problem behaviours, as did group membership, as expected. We did not a see an interaction of group membership with either anxiety or ADHD, indicating that the association between anxiety/ADHD and social skills is similarly moderated in both groups. SSRS scores predicted a significant amount of variance in GAF, and although not differentially so between the 22q11DS and control groups, it underscores the importance of social skills in the overall functioning of these children.

Table 4. Relationship of group and presence of ADHD with social skills

Criteria	Group			ADHD			Group × ADHD		
	R^2 change	β	f^2	R^2 change	β	f^2	R^2 change	β	f^2
SSRS – Total score	0.07	0.27**	0.08	0.07	−0.27**	0.08	0.007	0.09	0.007
SSRS – Problem behaviour score	0.04	−0.19	0.04	0.09	0.30**	0.09	0.000	0.002	0

*** $P < 0.001$, ** $P < 0.01$.

Table 5. Relationship of group and presence of any anxiety disorder with social skills

Criteria	Group			Any anxiety disorder			Group × any anxiety		
	R^2 change	β	f^2	R^2 change	β	f^2	R^2 change	β	f^2
SSRS – Total score	0.72	0.27**	**2.57**	0.13	−0.37***	**0.15**	0.001	0.03	0.001
SSRS – Problem behaviour score	0.04	−0.19	0.04	0.11	0.35***	0.12	0.001	−0.032	0.001

*** $P < 0.001$, ** $P < 0.01$.
Effect sizes that are medium or large are in bold.

Table 6. Relationship of group and GAF with social skills

Criteria	Group			SSRS-Total score			Group × total score		
	R^2 change	β	f^2	R^2 change	β	f^2	R^2 change	β	f^2
GAF	0.15	0.39***	**0.18**	0.15	0.40***	**0.18**	0.000	0.02	0
	Group			**SSRS – Problem score**			**Group × problem score**		
	0.14	0.37**	**0.16**	0.16	−0.40***	**0.19**	0.007	−0.09	0.007

*** $P < 0.001$, ** $P < 0.01$.
Effect sizes that are medium or large are in bold.

Discussion

The empirical literature on children with 22q11DS includes only a few reports on specific deficits in social skills in the domains of cooperation, assertion and responsibility (Kiley-Brabeck & Sobin 2006), and elevated social problems sub-scale mean score on the CBCL (Woodin *et al*. 2001; Bearden *et al*. 2005). Our findings substantiate the frequent and significant social skill difficulties these children face, an important finding, as social skills are crucial not just to success among peers, but also to academic functioning (Coie*et al*. 1990; Wentzel 1993).

Similarly, our finding of a correlation between SSRS and GAF attests to the association between social skills competence and overall functioning. Social skills are considered in the computation of GAF, so this association is not surprising, but it would be expected that improvement of social skills would result in better GAF in these children. Lower social skills competence and higher social skill problems in our 22q11DS cohort were also significantly correlated with higher rates of ADHD, anxiety disorders and internalising problems on the parent CBCL. With this, we provide evidence for the first time that social skills in children with 22q11DS are predicted by psychiatric/psychopathological manifestations. It is also plausible that poor social skills in these children with 22q11DS result in psychopathology such as ADHD and anxiety; however, based on the facts that both ADHD and anxiety are considered to be integral to 22q11DS and that empiric literature reports in typical children also supports the notion that anxiety and ADHD can lead to poor social skills (Ginsburg *et al*. 1998; Segrin 2000), we believe that anxiety disorders and ADHD more likely resulted in poor social skills in our cohort.

There were no correlations between social skills and IQ, or higher neurocognitive functions such as executive functioning within the 22q11DS group and thus it is unlikely that the social skill deficits that we saw in our cohort are associated with their lower intellectual abilities. A previous study reported a significant association between social skills and executive dysfunction in children with 22q11DS (Kiley-Brabeck & Sobin 2006), with initiation and monitoring predicting social skills (Kiley-Brabeck & Sobin 2006); however, the authors acknowledged the limitation of using a parent report as a measure of executive functioning. We administered the WCST to our participants, a well-validated measure of set shifting and cognitive flexibility and found no association between these executive functions and social skills. However, it is possible that neurocognition is indeed associated with social skills in children with 22q11DS, but due to the universal cognitive impairments that these children exhibit, we may not be able to detect differential associations within the group; alternatively this association may manifest at specific developmental stages, such as with the onset of major psychiatric illnesses such as schizophrenia, which is associated with a decline in both cognitive abilities and social skills. Thus, further longitudinal assessment of our cohort would yield important information in this regard.

Emotion recognition testing in our cohort revealed that children with 22q11DS had significant deficits in the perception and processing of emotions through facial expressions compared with the controls. This supports the previous studies that have reported abnormalities in face emotion recognition including face identity matching, face memory and face discrimination and the corresponding brain activation by fMRI in 22q11DS (Andersson *et al*. 2008; Campbell *et al*. 2010; Glaser *et al*. 2010). These deficits in children with 22q11DS could possibly be related to abnormalities in the temporal lobe circuits, particularly in the fusiform gyrus, which are involved

in visual recognition and social cognition (Barnea-Goraly *et al*. 2003; Glaser *et al*. 2007). In a small fMRI study of eight adults with 22q11DS with and without schizophrenia, hypoactivation of the right insula and the frontal regions was seen during visual processing of facial emotions (van Amelsvoort *et al*. 2006) and it was suggested that individuals with 22q11DS may have the ability to exhibit normal or enhanced affective responses to facial expression (intact affective empathy), but lack the necessary social and contextual abilities to interpret socio-emotional cues (lack of cognitive empathy). However, it is hard to tease out deficits integral to 22q11DS from those related to schizophrenia in that study. Our finding of impaired visual recognition of emotions in non-psychotic children with 22q11DS does not support the finding of intact affective responses in their paper. It is possible that the increased activation of the visual cortices in their study could represent over-recruitment of neurons rather than better face emotion recognition. Similarly, all the other studies (Andersson *et al*. 2008; Glaser *et al*. 2010) that have evaluated face emotion recognition in individuals with 22q11DS included both non-psychotic and psychotic individuals, thus making it difficult to separate social cognitive deficits because of psychosis from those that are central to 22q11DS. Because none of our subjects had psychotic symptoms, we provide evidence for the first time, that social cognition based on visual discrimination of emotions, is impaired in children with 22q11DS.

We are also the first to examine auditory discrimination of emotion in children with 22q11DS, relative to a healthy control group. Contrary to our expectations, we found that children with 22q11DS performed no differently than controls on auditory discrimination of social cues. We considered if this could be due to the higher rates of non-verbal learning deficits in these children as reported previously (Swillen *et al*. 1997, 2000), which would provide a relative strength in verbal abilities to these children, resulting in better auditory discrimination of all stimuli, including emotions. Approximately 20% of children in our cohort with 22q11DS have a split of more than 12 points on the verbal comprehension and perceptual organisation IQ indices, with the verbal being higher, one indicator of a non-verbal learning disability. However, our sample size is not large enough to apportion out these children and examine their auditory emotional perception and processing in relationship to the others who did not have this split in their IQ indices, but this remains a topic worthy of examination in the future. It is also to be noted that based on the medium and large effect sizes that were evident on the auditory emotion discrimination task, that we may be underpowered to detect differences between the 22q11DS and control groups.

An intriguing and surprising finding is the lack of correlation between the social cognitive measures (visual and auditory DANVA) and social skills (SSRS) in our study. A possible explanation could be that SSRS may not be capturing the specific deficits related to social cognition that are seen in children with 22q11DS. Another possibility is that the parent ratings on

the SSRS may be influenced by the rates of other psychological/medical problems that these children face continually; consequently parents may be underreporting the social problems. This is plausible, given that the differences between the 22q11DS and control groups were not as dramatic for the SSRS scores as they were for the other neurocognitive/behavioural domains (Table 1).

Implications for interventions

There is a need for assessment and interventions to improve social skill competence in children with 22q11DS. It is the clinical experience of the authors that this is frequently overlooked, both by the parents and caregivers, due in part to the more overt medical and cognitive/psychiatric problems that demand medical attention. Although this is not an intervention report, we propose an intervention model (Fig. 2) based on our confirmed associations between social skills and behaviour/emotional problems. Such interventions could improve social skills, and thereby overall functioning of children with 22q11DS. The model illustrates three pathways of interventions that we propose. Although our model includes improving SES, we acknowledge that improving a family's socio-economic circumstances is difficult and requires societal and economic reform, but nonetheless, clinicians caring for families with a child with 22q11DS should enquire into access to resources such as counselling or social skills training that the family may not have and make appropriate referrals to improve such access. An additional possibility is that interventions targeted at improving visual skills, especially visual attention and non-verbal learning deficits in children with 22q11DS may help in overcoming difficulties with social cognition, and thereby social skills, although we did not evaluate this in our study. It is also possible that improvements in neurocognition may result in social skills, despite the lack of an association between these domains in our study.

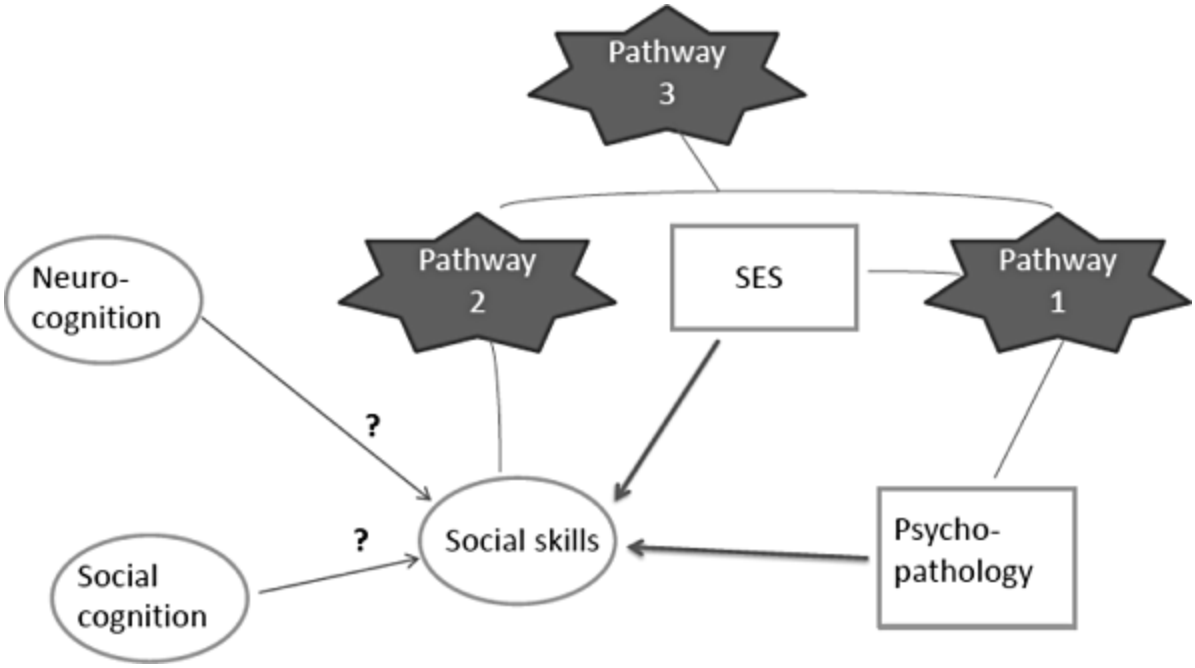

Figure 2. Diagram of proposed intervention pathways to improve social skills, based on confirmed associations. Intervention model to improve Social Skills in children with 22q11DS: Pathway 1 would treat psychopathology and improve the resources available to families of lower SES. Pathway 2 would directly intervene with social skills training. Pathway 3 would employ all the strategies used in Pathways 1 and 2. Improvement of social skills using these pathways of intervention should translate into improved global functioning. Based on our data, the impact of neurocognitive and social cognitive interventions upon social skills are unknown, but it would be reasonable to postulate that improvements in these domains may result in improvements in global functioning, even without an improvement in social skills.

Social skills training have been found to be effective in improving functionality in individuals with schizophrenia in the adult population (Tsang *et al*. 2009). Even though this may not be directly comparable with children and adolescents with 22q11DS, the implications of treating the social skill deficits in these children may have far-reaching effects, given their extraordinarily high psychosis risk. While we did not implement the interventions in our study population, the findings from our study would influence the future treatments that could be implemented for the social impairments in children with 22q11DS.

The limitations of our study are: (1) DANVA data were available only on a small number of participants and we did not assess other aspects of social cognition such as theory of mind; (2)

the SSRS has the limitation of assessing social competence rather than impairments, although it is a widely used research tool; (3) the SSRS may also fail to capture the type of deficits that children with 22q11DS experience, as anecdotally reported by parents in our study who completed the scale; and (4) the battery of neuropsychological assessments used in our study are not specifically designed to use in the 22q11DS population as there are no tests that are designed for this population that are available. However, all the assessments that we employed are normed for the paediatric population and have been used extensively in research studies and are well-validated.

In conclusion, children with 22q11DS were found to have significantly lower social skills and increased problem behaviours, and deficits in social cognition involving visual processing. The lower social skills and higher problem behaviours were associated with abnormalities in behaviour/emotion such as internalising symptoms, ADHD and anxiety disorders, but not with neurocognition, suggesting the possibility that treating the behaviour or emotional problems may facilitate the improvement of social skills in this population.

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