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ORIGINAL PAPER

Mother–Child Interaction as a Window to a Unique Social Phenotype in 22q11.2 Deletion Syndrome and in Williams Syndrome

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Abstract Mother-child interactions in 22q11.2 Deletion syndrome (22q11.2DS) and Williams syndrome (WS) were coded for maternal sensitivity/intrusiveness, child's expression of affect, levels of engagement, and dyadic reciprocity. WS children were found to express more positive emotions towards their mothers compared to 22q11.2DS children and those with developmental delay in a conflict interaction. During the same interaction, dyads of 22q11.2DS children were characterized by higher levels of maternal intrusiveness, lower levels of child's engagement and reduced reciprocity compared to dyads of typically developing children. Finally, 22q11.2DS children with the COMT Met allele showed less adaptive behaviors than children with the Val allele. Dyadic behaviors partially coincided with the distinct social phenotypes in these syndromes and are potential behavioral markers of psychopathological trajectory.

Keywords 22q11.2DS · Williams syndrome · Mother–child interaction · Behavior · *COMT* gene

Introduction

The 22q11.2 deletion syndrome (22q11.2DS) and Williams Syndrome (WS) are known neurogenetic autosomal dominant syndromes with distinct medical, cognitive, behavioral and psychiatric phenotypes. Both syndromes are caused by a microdeletion in the long arm of chromosome 22 (Morrow et al. 1995), and in the long arm of chromosome 7 (7q11.23) in WS (Pober 2010). Major physical anomalies associated with 22q11.2DS include cardiovascular anomalies (e.g., Tetralogy of Fallot and pulmonary atresia), hypernasal speech due to palate anomalies and hypocalcemia. Common physical manifestations in WS include supravalvular aortic stenosis, hypercalcemia and scoliosis. The mean IQ in 22q11.2DS is 75 (within the borderline range of intelligence) (Swillen et al. 1999). The mean IQ in WS is 60, with a typically higher verbal IQ than performance IQ (Pober 2010). Both syndromes have a high variability of IQ scores between subjects. They are associated with high rates of psychiatric disorders, including attention deficit/hyperactivity disorder, oppositional defiant disorder and phobias. Social anxiety disorder is more prevalent in 22q11.2DS, while specific phobia is more common in WS (Green et al. 2009; Leyfer et al. 2006). Up to one-third of individuals with 22q11.2DS develop schizophrenia-like psychotic disorders during adolescence and early adulthood, making 22q11.2DS the most

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commonly known genetic syndrome associated with schizophrenia (e.g., Gothelf et al. 2007).

Despite the significance of the social phenotype to the overall and longitudinal functioning of youth affected by these disorders (Gothelf et al. 2007), studies that assess the mechanisms underlying parent–child social/behavioral repertoire remain scarce. Several elements have been identified as having significant contribution to the formation of the child's social repertoire (Feldman 2007; Delaherche et al. 2012). Behaviors such as maternal sensitivity, maternal intrusiveness, child's social engagement with the mother, and dyadic reciprocity received most of the attention in this respect. Each of these constructs was shown to be individually stable in repeated observations from infancy to adolescence (Feldman et al. 2013; Feldman 2010), and to predict a multitude of outcomes, including social competence and reduced aggression with peers (Feldman and Masalha 2010), less psychopathology and lower depression in adolescence (Feldman 2010), and better cognitive development (Feldman and Eidelman 2009). Starting in middle childhood, social/behavioral factors are also predicted by the functioning of core physiological systems such as the autonomic nervous system (Feldman and Eidelman 2009), and the human stress response (Feldman et al. 2014a, b).

Individuals with WS often display a typical maladaptive and over-friendly social phenotype that is a core characteristic of the syndrome (Järvinen-Pasley et al. 2008). WS youth are frequently regarded as significantly more people-oriented (hyper-social), intensive, empathic, and gregarious, compared to TD children and individuals with other developmental disabilities (Meyer-Lindenberg et al. 2006; Martens et al. 2008; Pober 2010.) Consequently, parent–child dyads that involve WS youth were reportedly characterized by twice as much parental involvement and positive reinforcement compared to dyads of children with Prader–Willi syndrome (Ly and Hodapp 2005).

Conversely, individuals with 22q11.2DS are known to be shy, socially inhibited, tend to avoid social encounters, and frequently exhibit restricted emotional expression and deficient ability to understand others' intentions (Ho et al. 2012; Schonherz et al. 2014; Swillen et al. 1999). Children with 22q11.2DS are also reported by caregivers as being less cheerful and pleasant, less likely to stay with an activity for a long time, and less capable of responding flexibly to changes in comparison to their healthy siblings and TD controls (Antshel et al. 2007; Angkustsiri et al. 2014).

These findings further substantiate the claim that different genetic backgrounds lead to alterations in the child's functioning, altered parental response, and variance in parent–child interaction, despite similar general cognitive abilities.

Notwithstanding the copious studies uncovering social manifestations of children and adolescents with neurogenetic syndromes, the reports in the literature rely mostly on parents' and teachers' self-reports which are inherently subjective. Thus, sequential investigational practices that are more objective and less prone to reporter's bias, that are more ecologically valid, and that refer to behaviors that are central to the child's socio-emotional functioning are much needed.

Moreover, studying parent–child interaction in the setting of genetic syndromes allows us to draw links between genetic polymorphisms in designated single-nucleotide polymorphisms (SNPs) and socio-behavioral phenotypes. For example, 22q11.2DS is caused by a homozygous deletion in chromosome 22, and the classical 3 Mb 22q11.2 deletion consists of ~60 genes (Drew et al. 2011). Among these genes is the *catechol-O-methyltransferase* (*COMT*), which plays a critical role in the metabolic degradation of dopamine and norepinephrine, and is associated with behavioral symptomatology (Lachman et al. 1996), and social learning (Set et al. 2014). The *COMT* gene contains a $Val^{108/158}$Met polymorphism that encodes for two enzyme variants. All individuals with 22q11.2DS are haploinsufficient for *COMT,* i.e., carry only one copy of the *COMT* gene instead of two copies. Since the *COMT* Met variant codes for a less active COMT enzyme, 22q11.2DS individuals with the *COMT* Met carriers are deficient in *COMT* enzyme activity and are thus putatively exposed to unusually high brain dopamine levels from an early age (Gothelf et al. 2014). Consequently, they are allegedly at higher risk of psychiatric disorders than 22q11.2DS carriers of the *COMT* Val allele (Bearden et al. 2005; Gothelf et al. 2008). However, the existing findings are inconsistent and rely mostly on caregivers' reports, with a paucity of objective measures, thus calling for further investigation using micro-level coding of patients' social behavior.

Towards this end, we aimed to characterize patterns of mother–child interaction in 22q11.2DS and WS participants. Given the different social phenotypes, we expected to find unique behavioral/dyadic configurations in each syndrome. Our specific hypotheses were: (1) *Child behavior*: children with WS would exhibit greater affective expression towards their mothers compared to children with 22q11.2DS and children with developmental disability (DD), and a WS child's engagement in the interaction would be similar to that of a TD child. Conversely, 22q11.2DS children would be expected to show less engagement during interaction with their mothers compared to the WS and TD children; (2) *Maternal behavior*: mothers of children with WS would show higher levels of sensitivity compared to mothers of children with 22q11.2DS, whereas the latter would be expected to show

higher levels of intrusiveness but lower levels of sensitivity compared to mothers of TD children; (3) in line with existing developmental literature, we assumed that behavioral problems and lower adaptive skills of all participants would be associated with higher levels of maternal intrusiveness, but with lower levels of maternal sensitivity, child engagement, and dyadic reciprocity; (4) finally, we hypothesized that the *COMT* Met allele would be associated with attenuated dyadic reciprocity in 22q11.2DS children.

Methods

Participants

The study included a total of 82 dyads, of them, 24 children with 22q11.2DS, 18 children with WS, 20 children with idiopathic DD (IQ-matched to the two clinical groups) and 20 TD (controls). The characteristics of the four groups are presented in Table 1. The three clinical groups were between 7 and 15 years of age. The TD subjects were matched to the clinical groups in terms of mental age (MA; see statistical analyses and supplementary 1 for specifics for mental age matching), and their chronological age (CA) ranged between 4 and 12 years. MA was calculated according to the formula: IQ = MA/CA * 100. Eighteen of 25 children with 22q11.2DS (72 %) underwent one or more major surgeries as follows: cleft palate repair (pharyngeal flap) = 15, cardiovascular procedures = 5 (repair of Tetralogy of Fallot or ventricular septal defect = 4 and aortic arch repair = 1), and tracheostomy, scoliosis repair and ventricular shunt = 1 each. Six of the 18 children with WS (33.3 %) underwent major surgeries as follows: repair of supravalvular aortic stenosis or pulmonary stenosis = 4, and ventricular shunt and colectomy = 1 each.

Maternal age ranged between 38 and 45 years, and mothers of DD children were found to be significantly older than mother of TD children. Most mothers were married to the child's father, and completed at least high-school level education (12 years or more), and the groups did not differ on the basis of these variables. The psychiatric history of the parents was collected using a checklist of common potential psychiatric disorders and a short interview. The following psychopathologies were reported in parents of 22q11.2DS probands: history of major depressive disorder (two mothers), bipolar affective disorder and generalized anxiety disorder (one mother each), and attention deficit/hyperactivity disorder (one father). The following psychopathologies were reported in the parents of the WS probands: attention deficit/hyperactivity disorder (three mothers), history of major depressive disorder, dysthymia and specific phobia (one mother each), and attention deficit/hyperactivity disorder (one father). In the parents of the WS probands the following psychopathologies were reported: attention deficit/hyperactivity disorder (three mothers), history of major depressive disorder, dysthymia and specific phobia (one mother each), attention deficit/hyperactivity disorder (one father).

The WS and 22q11.2DS participants were recruited from the Behavioral Neurogenetics Center at a large tertiary referral center in Israel. The diagnosis of WS and 22q11.2DS was confirmed in all participants by the fluorescent in situ hybridization test. Participants with idiopathic DD were recruited from schools for special education for children and adolescents with DD. TD controls were recruited through advertisements within the local community. They were all students in mainstream classes and none had a major psychopathology: data on their cognitive abilities (i.e., IQ score) are lacking because of our IRB restraints on administering assessment tests to TD children. The study was approved by the Institutional

Table 1 Maternal and child's characteristics in the four study groups

	WS	22q11.2DS	DD	TD	ANOVA F
N	18	24	20	20	
Maternal age, years	41.94 (6.73)	42.33 (4.43)	45.80 (8.18)	38.20 (5.93)	$F(3,78) = 4.76$**
Marital status (Married/Not)[a]	17/0	18/4	15/4	19/1	
Mother's education (Completed High-School/Not)[a]	16/1	20/2	17/2	20/0	
Child's age, years	11.96 (2.33)	11.41 (1.96)	10.86 (2.72)	7.82 (2.38)	$F(3,78) = 12.33^{\dagger}$
Mental age	7.82 (1.36)	9.5 (2.01)	7.83 (2.00)	7.32 (2.38)	$F(3,74) = 3.75$*
IQ	67.63 (8.78)	83.57 (11.95)	73.84 (9.52)		$F(2,75) = 11.70^{\dagger}$
Gender (M/F)	9/9	$17/7^{\dagger}$	$14/6^{\ddagger}$	11/9	

Mean (SD)

* $p < 0.05$; ** $p < 0.01$; † $p < 0.001$; ‡ X2 analysis, $p < 0.05$

[a] Data from several mothers is missing, X2 analysis, p = ns

Review Board. After providing a complete description of the nature of this study, we obtained written informed consent from the parents of all participants.

Cognitive, Behavioral and Adaptive Functioning Assessments

The Full Scale IQ (FSIQ) score of children in the three clinical groups was assessed using the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Green et al. 2009). Mothers were asked to complete the child behavioral checklist (CBCL) questionnaire (Rescorla 2005). Two versions of the questionnaire were used, one designed for children between 1.5 and 5 years of age, and the other for school-aged children between 6 and 18 years of age. Both versions yield standardized scores of externalizing behaviors, internalizing behaviors, and a total CBCL score which is derived from the sum of the subscales. An externalizing score for the 1½–5 year age group was calculated from the attention problems and aggressive behavior subscales, and an internalizing score was calculated from the emotional reactivity, anxious/depressed, somatic complaints, and social withdrawal subscales. The total score was calculated from the sum of the externalizing and internalizing scores and the sleep and other problems subscales. The externalizing score for the 6–18 year age group was calculated from the rule-breaking and aggressive behavior subscales, and the internalizing score was calculated from the anxious/depressed, withdrawn/depressed, and somatic complaints subscales. The total score was calculated from the sum of the externalizing and internalizing scores and the social, attention, thought, and other problems subscales.

The participants' adaptive behavior was assessed using the Vineland Adaptive Behavior Scale (VABS; Sparrow and Cicchetti 1985). The VABS was found to be a valid measure for assessing daily skills, both for TD children as well as for those with clinical disorders or developmental delays (Schneider et al. 2014).

Assessment of Mother–Child Interaction

Parents and children were asked by the experimenter to engage in a semi-structured social interaction during a visit to the lab. The mothers and children were instructed to first discuss a conflict between them for 8 min, and then to freely plan a fun day together for another 8 min. Dyadic interactions started when a mother and her child were sitting in front of each other in a quiet room with the door closed and the experimenter waiting outside. All interactions were videotaped. The interactions were coded offline, using the Coding Interactive Behavior (CIB) Manual (Feldman 1998), a well-validated tool with good psychometric properties.

This global rating system for adult–child interactions includes 42 scales, which are grouped into several theoretically meaningful constructs. Coding was conducted by two trained raters who were blind to study group allocation. Facial features in children with 22q11.2DS and WS are not necessarily dysmorphic but are more typical and our experience shows that raters that are not expert do not easily distinct between the two syndromes. Yet, we do recognize now the potential bias stemming from the distinct facial features of the syndromes and mention it as a potential limitation of our study.

Coders were trained by the person responsible for the global teaching of the CIB technique who had vast experience and dozens of trainees globally. Inter-rater reliability was calculated based on the independent coding of two observers of randomly chosen 15 % of the sample. The percentage of agreement, calculated as the number of agreements divided by the mean number of events, reached 92 % ($r = 0.92$). Cases of disagreement between coders were resolved by discussing the behavior until agreement was reached.

Constructs, codes, and internal consistency were as follows: *maternal sensitivity* ($\alpha = 0.86$), including maternal acknowledgement of the child's communications, elaboration of the child's suggestions/ideas, positive affect and proximity, appropriate range of affect, affectionate touch, resourcefulness and creativity, consistency of style, and supportive presence; *maternal intrusiveness* ($\alpha = 0.81$), including interruptions and overriding the child's stream of activity or communication, negative parental affect, hostility, and criticism; *mother's dialogical skills* ($\alpha = 0.82$), including acknowledgement of the child's position and perspective on any given matter; empathy with the child's feelings, emotions, or point of view, and enabling the child to freely express himself/herself; *child engagement* ($\alpha = 0.85$), including positive affect, self-confidence, initiation, creativity, attention, cooperation, motivation, and child's belief that he/she can benefit from the interaction; *child withdrawal* ($\alpha = 0.70$), including withdrawal from and avoidance of any encounter with the parent; *dyadic reciprocity* ($\alpha = 0.86$), including addressing aspects of the interaction, such as the mother and her child engaging in give-and-receive interactions that are sensitive to micro-level verbal (e.g., child mutters "Oh, No!") and nonverbal (e.g., gaze aversion, quick smiles, gestures, heavy breathing) cues, dyad adaptations to each other's needs and communications, and interactions that are fluent, harmonious, and rhythmic; *tension* ($\alpha = 0.72$), including the child's negative affect, emotional liability, and tension; *child's expression of affect towards parent* ($\alpha = 0.70$), including the level of the child's verbal expression, facial and bodily gestures as they reflect affection towards the mother. All eight of those constructs were used

for group comparisons for the conflict interaction, and all but the *child's expression of affect* were used for the positive/fun interaction.

COMT Genotyping

COMT Val158Met polymorphism (rs4680) was genotyped by the C25746809-50 TaqMan kit (Applied Biosystems Incorporated, Foster City, CA) using the ABI 7000 instrument. All individuals with 22q11.2DS are hemizygote for the *COMT* gene because they carry one copy of the gene instead of two copies. In addition to the FISH test, the size of the deletion in 22q11.2DS was determined using Multiplex Ligation Probe Amplification (MLPA) in 23 of the 24 children with 22q11.2DS. Of those 23 children, 19 (82.6 %) carried the 3 Mb typically deleted region, 2 had a deletion size of 1.5 Mb, and one each had a 2 Mb deletion and a larger than 3 Mb deletion. The size of the deletion in 22q11.2DS was determined using Multiplex Ligation Probe Amplification (MLPA) in 23 of the 24 children with 22q11.2DS. Of the 23 children 19 (82.6 %) carried the 3 Mb typically deleted region, in two children the deletion size was 1.5 Mb, and a 2 Mb and a larger than 3 Mb deletion was present in one children each.

The *COMT* Met and Val subgroups were similar in terms of male/female ratio (7/4 vs. 9/3 in the Val and Met groups, respectively), chronological age (11.08 vs. 12.01 years; χ^2, p = ns), and FSIQ scores (80.36 vs. 84.64; T, p = ns). Finally, genetic assessment revealed that all but one of the mothers of children with 22q11.2DS who were genotyped did not carry the deletion, and therefore 22 out of 23 of those children qualify as have a de-novo deletion.

Statistical Analyses

Two steps were taken in order to deal with the group differences in MA and FSIQ scores. First, statistical analyses were conducted while controlling for MA. Second, each analysis was done twice, once on the larger sample of 82 subjects (which differed in FSIQ, with 22q11.2DS having the highest score, then DD, and finally WS), and once on a smaller sample of 70 subjects with the three clinical groups that were matched for FSIQ scores. Following, we detail the analyses conducted while controlling for MA, and we mention the findings in the smaller sample of 70 subjects only in cases when results vary from those in the main analysis (See supplement 1 for further details).

Several multivariate analyses of co-variance (MANCOVA) were employed to compare between the three study groups and the control group in behavioral symptoms, adaptive functioning, and mother–child behaviors in the conflict and fun interactions. MA was held as covariant. Univariate analysis of co-variance (ANCOVA) and post hoc Bonferroni comparisons were computed in cases of statistical significance. Partial correlations were used to draw associations between mother–child behaviors and adaptive skills/symptomatology scales (i.e., the VABS and CBCL, respectively). Hierarchal linear regressions were employed to predict variation in selected mother–child behaviors based on group, adaptive skills, and symptomatology. Finally, Independent t tests were calculated to compare mother–child behaviors (averaged across the conflict and fun interaction) between Val and Met allele carriers of *COMT* rs4680 among the 22q11.2DS children.

Results

Behavioral and Adaptive Functioning

MANCOVA analysis of CBCL scores revealed a group main effect, $F_{(24,180)} = 4.12$, $p = 0.000$. Compared to the TD group, the three clinical groups showed significantly higher scores in the variable "social problems" as well as in the three global constructs: externalizing behavior, internalizing behavior, and total CBCL score. The clinical groups did not differentiate among themselves in any of the CBCL scales. The DD group scored higher on "withdrawn/depression" than the TD group (see supplement 1 and supplementary Table S1 for descriptive data).

MANCOVA analysis of the VABS scores also revealed a group main effect, $F_{(9213)} = 3.15$, $p = 0.001$. Further analysis showed that the TD group exhibited significantly higher scores on each of the four scales of Communication, Daily Skills, Socialization, and General Adaptive Behavior compared to the three clinical groups. The 22q11.2DS group scored significantly higher than the WS group on each of these scales, whereas the DD group did not differ from either the WS or 22q11.2DS groups. Those findings persisted for the analysis conducted on the smaller sample of 70 IQ-matched subjects (see supplement 1 and supplementary Table S2).

Mother–Child Interaction

MANCOVA analysis showed that overall dyadic behaviors in the TD group differed from those of the other three clinical groups, $F_{(45,168)} = 2.36$, $p = 0.000$.

Conflict Interaction

Further analysis revealed that mothers of children with 22q11.2DS showed higher levels of intrusiveness compared to mothers of TD children. While they also showed greater intrusiveness than the mothers of WS and DD children, the difference did not reach a level of significance

in this construct. The mothers' dialogical skills construct was higher among the mothers of TD children compared to the mothers of the WS and DD groups. The child's engagement was lower in the 22q11.2DS group compared to the TD group. The child's expression of affect towards mothers was higher among the WS children compared to the 22q11.2DS and DD children, but it did not differ from that of the TD children. Finally, the TD dyads were characterized by a higher level of dyadic synchrony compared to the 22q11.2DS and DD groups, but they did not differ from those observed in the WS group (see Table 2).

Fun Interaction

Maternal sensitivity was lower among the mothers of the 22q11.2DS children compared to the mothers of the TD group. The dialogical skills construct of the TD mothers was higher than the 22q11.2DS mothers. The child's engagement and dyadic reciprocity scores were higher among the TD subjects compared to the three clinical groups (Table 2).

Mother–Child Behaviors, Behavioral Symptoms and Adaptive Repertoire

Two behavioral composites, child's engagement and dyadic reciprocity (calculated as the mean score of each behavior in both the conflict and fun interactions), were found to associate with the subscales and the total/general scores of the CBCL and VABS measures. As can be seen in supplementary Table S3, the child's behavioral problems inversely correlated with his/her engagement and level of dyadic reciprocity. Similarly, higher levels of the child's engagement and dyadic reciprocity were positively correlated with adaptive behaviors across all of the VABS domains, i.e., Communication, Daily Skills, Socialization, and General Adaptive Behavior.

Predicting Mother–Child Behaviors

Two linear regression models were calculated to predict the child's engagement (mean score of the conflict and fun interactions) and dyadic reciprocity. Variables were entered in four steps: the subjects' MA was entered in the first step, group (clinical diagnosis) in the second step, general adaptive composite (VABS general) in the third step, and total behavioral problems (CBCL total) in the fourth step.

Overall, the model predicted 17 % of the variance in child engagement, $R^2total = 0.17$, $F_{(4,71)} = 3.47$, $p = 0.01$, and group and total behavior problems each made unique contributions to the model: group: $\beta = 0.07$, $p =$ ns, $R^2change = 0.09$, $Fchange_{(1,69)} = 7.22$, $p < 0.01$; total behavioral problems: $\beta = -0.25$, $p = 0.06$, $R^2change = 0.04$, $Fchange_{(1,67)} = 3.61$, $p = 0.06$. The contribution of general adaptive skills did not reach a level of significance: $\beta = 0.16$, $p =$ ns, $R^2change = 0.03$, $p =$ ns.

The model predicted 26 % of the variance in dyadic reciprocity, $R^2total = 0.26$, $F_{(4,71)} = 5.99$, $p < 0.001$, and each

Table 2 Mother–child interaction in the conflict and fun sessions

	WS	22q11.2DS	DD	TD	ANOVA F	Group Differences
Conflict						
Maternal sensitivity	2.90 (0.96)	2.72 (0.66)	2.85 (1.13)	3.33 (0.80)	F(3,71) = 1.37	
Maternal intrusiveness	2.21 (0.91)	2.60 (0.75)	2.19 (0.82)	1.81 (0.62)	F(3,71) = 2.59*	22q11.2ds > td
Maternal dialogical skills	2.17 (0.48)	2.38 (0.88)	2.34 (0.96)	3.09 (0.77)	F(3,71) = 4.55†	td > ws,dd
Child engagement	2.72 (0.83)	2.20 (0.42)	2.42 (0.83)	2.77 (0.81)	F(3,71) = 3.21*	td > 22q11.2ds
Child expression of affect	3.12 (0.88)	2.32 (0.86)	2.30 (0.62)	2.71 (0.75)	F(3,71) = 4.23†	ws > 22q11.2ds,dd
Child withdrawal	1.91 (0.77)	2.37 (0.87)	1.87 (1.06)	1.53 (0.70)	F(3,69) = 2.28	
Dyadic reciprocity	2.86 (1.04)	2.80 (0.79)	2.75 (1.06)	3.62 (0.92)	F(3,71) = 3.84*	td > 22q11.2ds,dd
Tension	1.99 (0.83)	1.85 (0.74)	2.01 (0.74)	1.62 (0.60)	F(3,69) = 1.06	
Fun						
Maternal sensitivity	2.52 (0.74)	2.28 (0.58)	2.62 (0.66)	3.04 (0.72)	F(3,69) = 3.33*	td > 22q11.2ds
Maternal intrusiveness	2.0 (0.91)	1.84 (0.68)	1.74 (0.50)	1.63 (0.63)	F(3,69) < 1	
Maternal dialogical skills	2.41 (0.64)	2.29 (0.67)	2.48 (0.80)	3.06 (0.93)	F(3,69) = 3.60*	td > 22q11.2ds
Child engagement	2.72 (0.80)	2.75 (0.90)	2.72 (0.71)	3.65 (1.00)	F(3,69) = 4.95†	td > ws,22q11.2ds,dd
Child withdrawal	1.91 (0.77)	2.10 (1.1)	1.87 (1.06)	1.53 (0.70)	F(3,69) < 1	
Dyadic reciprocity	3.04 (0.83)	3.10 (0.95)	3.07 (0.82)	3.90 (0.87)	F(3,71) = 4.10†	td > ws,22q11.2ds,dd
Tension	1.98 (0.84)	1.84 (0.74)	2.01 (0.73)	1.62 (0.61)	F(3,69) = 1.06	

Mean (SD)

* $p < 0.05$; † $p < 0.01$; Bonferroni pos-hoc

variable made a unique contribution to the model: group: $\beta = 0.01, p = \text{ns}, R^2change = 0.13, Fchange_{(1,69)} = 10.26$, $p = 0.002$; general adaptive skills: $\beta = 0.28$, $p = 0.07$, $R^2change = 0.07$, $Fchange_{(1,68)} = 6.12$, $p = 0.016$; and total behavior problems: $\beta = -0.29, p = 0.02, R^2change = 0.06, Fchange_{(1,67)} = 5.57, p = 0.02$.

COMT Genotype and Mother–Child Interaction

For this analysis, each behavior was averaged across the fun and conflict interactions (Fig. 1). Independent t-tests showed that the 22q11.2DS *COMT* Met subgroup was characterized by lower maternal sensitivity ($t_{(21)} = 2.51, p = 0.02$), lower maternal dialogical skills ($t_{(21)} = 2.28$, $p = 0.04$), and less expression of the children's emotions to their mothers ($t_{(21)} = 2.18$, $p = 0.04$) compared to the 22q11.2DS *COMT* Val subgroup. For this analysis, each behavioral construct was averaged across the fun and conflict interactions (Fig. 1). These findings did not hold a Bonferroni correction, and this is now mentioned as part of the limitations of the study. Genotype was not related to any other behavioral constructs (i.e., maternal intrusiveness, child engagement, child withdrawal, dyadic reciprocity, and tension). These results are in line with some previous studies from our group and those of others, suggesting that 22q11.2DS *COMT* Met carriers are more severely affected in terms of cognition and behavior compared to 22q11.2DS Val carriers (Gothelf et al. 2005; Schneider et al. 2012). Other studies, however, did not find such an association between *COMT* genotype and the cognitive and psychiatric phenotype of 22q11.2DS (Stoddard et al. 2012; Monks et al. 2014).

Discussion

To the best of our knowledge, this study is among the first to investigate patterns of mother–child interaction in children and adolescents with 22q11.2DS and WS. Given that the current literature highlights the importance of early social experiences in determining an individual's socio-emotional functioning (e.g., Feldman et al. 2013; Feldman 2010), this study—characterizing mother–child social interaction in 22q11.2DS and WS samples—has the potential to advance our understanding of the reciprocal influences between genetic factors, early life experiences, and development.

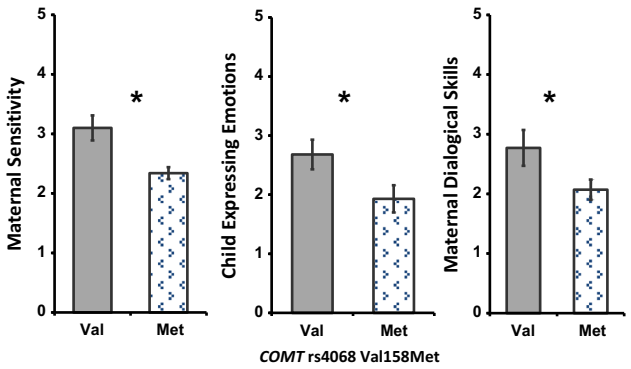

Fig. 1 *COMT* genotype (Val158Met) in children with 22q11.2DS is associated with mother–child behaviors (average score of the fun and conflict interactions)

Our first hypothesis of greater expression of affect in WS was partially confirmed. First, children with WS expressed significantly more positive emotions towards their mothers compared to children with 22q11.2DS and those with DD, as expressed by their being more affectionate, by smiling more and by touching their mothers more, as well as displaying a greater willingness for proximity. These findings are in line with the enhanced social repertoire that characterizes individuals with WS (Doyle et al. 2004; Klein-Tasman and Mervis 2003). Such intense emotional expressiveness during conflict genuinely reflects the maladaptive, exaggerated and, at times, inappropriate social phenotype that is a core characteristic of the syndrome. The heightened expression of positive emotionality in the WS group was evident despite the absence of any statistical differences between the three clinical groups in maternal sensitivity, counter to our a priori assumption (hypothesis #2). Surprisingly, contrary to our hypothesis, we did not find heightened expression of positive emotionality in the WS group. This may be explained by the subjects' characteristics (i.e., parents volunteering to participate in the study are arguably more involved and child-oriented than their average counterparts), or due to the relatively small sample size and large variability (standard deviation) in the 'maternal sensitivity' construct that hypothesized differences between the groups.

Second, despite the increased social appetite of children with WS (Jones et al. 2000), and contradictory to our initial assumption, they were similarly engaged in the social interaction as the DD and TD subjects, with the 22q11.2DS children showing poorer engagement. The over-involvement of children with WS was manifest through active initiation of conversation and their willingness to cooperate with the mother. This is in line with previous studies showing that WS children tend to rate others as being more attentive and willing to form social connections than TD children (Bellugi et al. 1999; Jones et al. 2000). WS individuals encourage social encounters by staring at people (Mervis 2003), or by using rich, dramatic and exaggerated vocabulary and vocal expression that is meant to attract the listener and to get him/her involved in the interaction (Jones et al. 2000; Losh et al. 2001; Pearlman-Avnion and Eviatar 2001; Reilly et al. 2004). Third, supporting our first and second hypothesis, WS group exhibited similar levels of dyadic synchrony as the TD group, while both the

22q11.2DS and DD dyads were characterized by less mother–child reciprocity. Mothers and their WS children were shown to have the adequate eco-system to express themselves, they referred to each other, and the interaction was suave. This is most likely due to the high social skills and empathic capacities of WS children (Dykens and Rosner 1999; Klein-Tasman and Mervis 2003), which differentiates them from children with similar IQs but without the genetic deficiency (Sullivan and Tager-Flusberg 1999).

In contrast, there were high levels of maternal intrusiveness, low levels of child engagement, and lower dyadic reciprocity between the 22q11.2DS dyads compared to the TD dyads. Children with 22q11.2DS also expressed less positive emotionality towards their mothers during the conflict session than the WS children. It is most likely that higher maternal intrusiveness takes place (or is reinforced) due to the unique social phenotype of 22q11.2DS, specifically, the extreme shyness, withdrawn behavior and avoidant social repertoire (Gothelf et al. 2008). That clinical group had lower child engagement, and the level of maternal intrusiveness inversely correlated with children's level of engagement, a pattern that replicates the results in pediatric samples with developmental delays (Spiker et al. 2002). This can be explained in two different ways. First, the inflexible temperament and social rigidness that characterize many 22q11.2DS children shapes the nature of the dyadic interaction a priori. Moreover, 22q11.2DS children are less likely to express their emotions, to smile, to socially engage with parents, and to initiate joint activities or to keep partaking in such activities over time (Antshel et al. 2007). That, in turn, reinforces the child's communication difficulties, which leads to greater efforts on the mother's part to bring the child back into the social milieu. Given that increased maternal guidance may be used to compensate for a child's social deficits, further investigation into this particular measure is warranted in order to identify the child's characteristics that shape this construct.

A second explanation might be attributed to the cleft anomalies that are present in ~75 % of 22q11.2DS individuals, which leads to significant speech difficulties and causes a major communication problem (Golding-Kushner et al. 1985), in addition to undermining their ability to establish social skills that are based on eloquent verbal communication (Robertson and Ellis Weismer 1999). However, given the heterogeneity of speech/verbal impairments characteristic of individuals with 22q11.2DS, a combination of factors may underlie their social difficulties. Regardless of the etiology of the social impairment, again, the parent senses the need to be active and to assume the role of mediator between the child and the social surroundings.

Finally, the 22q11.2DS dyads exhibited less synchrony than the TD dyads. Mothers were more dominant in the interaction and spoke more, while the children were less responsive to the social cues. The interactions were less fluent and included more periods of silence. Developmental literature has identified several characteristics in children that thwart attempts to form a coherent, mutually attentive dyadic relationship, including low initiative, abnormal eye contact pattern, shyness and social anxiety, stereotypic/repetitive behavior, unclear speech and difficulties in pragmatic use of the language—all of which are core aspects of 22q11.2DS (Debbané et al. 2010; Gothelf 2007; Shprintzen 2008).

Interestingly, whereas the clinical groups differed from the TD group in both the conflict and fun sessions, differences between the clinical groups themselves emerged only in the conflict interaction. This pattern reflects a widely accepted notion that parent–child interaction intensifies in strenuous circumstances in a way that facilitates the discrimination between clinical groups (Keren et al. 2001). In terms of a positive mother–child interaction, the clinical groups differed from the TD dyads in levels of child engagement and dyadic reciprocity, showing lower levels in these two behavioral constructs. The reported findings further support the idea that disturbed mother–child dyads in pediatric populations with developmental delays are often caused by the child's difficulty to adequately communicate him/herself. Such difficulties lead to greater efforts from the caregivers' side to bring the child "back on track" and help him/her integrate into the social setting. By doing so, mothers tend to dictate and dominate the interaction, which unintentionally leads to less coordinated and less synchronous interaction than the one observed in TD children. Recently published research conducted by one of the authors of the current study (RF) has demonstrated once again the validity of behavioral coding techniques for characterizing parent–child interaction in non-neurogenetic disorders, such as autism spectrum disorders (Hirschler-Guttenberg et al. 2014; Feldman et al. 2014a, b).

Furthermore, in line with our third hypothesis, the child's engagement in the interaction, and mother–child dyadic reciprocity were independently associated with his/her symptomatology and adaptive repertoire across all four study groups. The linear regression analysis revealed that group identity (clinical diagnosis), adaptive skills (VABS general scores), and total behavior problems (CBCL total) served as a unique predictor of dyadic reciprocity (explaining 26 % of overall variance). With respect to the child's engagement, clinical diagnosis and total behavior problems emerged as unique predictors and the total explained variance nests around 17 %. Taken together, these findings correspond with existing literature by showing that maternal attunement to the child's signals, the child's engagement and participation, and the behavioral symptoms

and adaptive repertoire are all associated with socio-emotional development and the emergence of debilitating psychiatric conditions in healthy and at-risk populations (Feldman and Eidelman 2009; Gothelf et al. 2007; Smith et al. 2008).

Finally, relating the fourth and last hypothesis, we detail differences in mother–child behaviors as a matter of *COMT* functionality, with Val allele carriers showing more adaptive dyadic interactions. This is the first time that a distinct genetic marker in 22q11.2DS, which is known to play a major role in the social manifestation of the disorder, is being associated with specific behaviors that have been shown to contribute to a child's socio-emotional development. Maternal sensitivity and the child's emotional expressivity emerged as important behavioral constructs that differentiate between Val versus Met allele carriers in the 22q11.2DS sample.

Of note, other genes, e.g., the proline dehydrogenase, may contribute independently or interactively to the social-behavioral phenotypes of 22q11.2DS in addition to *COMT* (for review, see Karayiorgou et al. 2010). As for WS, future studies should search for genotype-social phenotype interactions in candidate genes from the 7q11.23 deleted region causing WS, such as *GTF2IRD1* and *GTF2I* that were associated with the social phenotype in WS in humans as well as in mice models (Karmiloff-Smith et al. 2012).

Limitations of the study relate to the unique facial features of each of the syndrome that might have influences coders' blindness to group identity. In addition, assessing IQ in WS is questionable, as these patients are often characterized by distinct cognitive profile that manifests in a gap between verbal and performance IQs and may therefore bias findings of associations between IQ and verbal-dependent measures. Extending beyond *COMT* to test also other genetic markers that are relevant to WS has the potential to advance our understanding of gene-behavior correlates in these patients. The significance findings associating allelic variation with social behaviors were not corrected for multiple comparisons (i.e., Bonferroni correction) and should therefore be considered with some caution.

Comparing 22q11.2DS to other clinical groups and TD controls, we found that the dyadic relations between children with 22q11.2DS and their mothers are characterized by greater disturbances. These findings suggest that dyadic psychotherapy should be considered in families with 22q11.2DS children. During the dyadic therapy sessions mothers will have the opportunity to be guided on how to increase their child's social engagement in a constructive and non-intrusive manner (Leclère et al. 2014). Importantly, the CIB has been shown to be a useful tool for assessing improvement in mother–child interaction following dyadic psychotherapy (Keren et al. 2001).

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