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Social Cognition Impairments in 22q11.2DS Individuals With and Without Psychosis: A Comparison Study With a Large Population of Patients With Schizophrenia

Tommaso Accinni[1], Antonino Buzzanca[1], Marianna Frascarelli*[,1], Luca Carlone[1], Francesco Ghezzi[1], Georgios D. Kotzalidis[2], Paola Bucci[3], Giulia Maria Giordano[3], Nicoletta Girardi[1], Alessia Panzera[1], Simone Montaldo[1], Martina Fanella[1], Carlo Di Bonaventura[1], Carolina Putotto[4], Paolo Versacci[4], Bruno Marino[4], Massimo Pasquini[1], Massimo Biondi[1], and Fabio Di Fabio[1]

[1]Department of Human Neurosciences, Sapienza University of Rome, Faculty of Medicine and Dentistry, Rome, Italy; [2]Department of Neurosciences, Mental Health and Sensory Organs, Sapienza University, Faculty of Medicine and Psychology, Rome, Italy; [3]Department of Psychiatry, Campania University "Luigi Vanvitelli," Naples, Italy; [4]Department of Pediatrics, Sapienza Univerisity of Rome, Rome, Italy

*To whom correspondence should be addressed to: Piazzale Aldo Moro 5, 00185 Rome, Italy; Tel. +39-0649914591, e-mail: marianna.frascarelli@gmail.com

Background: **22q11.2 Deletion Syndrome (22q11DS) represents one of the most important genetic risk factors for schizophrenia (SCZ) and a reliable biological model to study endophenotypic characters of SCZ. The aim of the study was to investigate Social Cognition impairments in subjects with 22q11.2DS compared to a considerable sample of schizophrenic patients.** ***Methods:*** **Forty-four individuals with 22q11.2DS (DEL) and 18 patients with 22q11.2DS and psychosis (DEL_SCZ) were enrolled; these groups were compared to 887 patients with schizophrenia (SCZ) and 780 healthy controls (HCs); the latter groups were recruited by the Italian Network for Research on Psychoses (NIRP) to which our Centre took part. Social cognition was evaluated through The Awareness of Social Inference Test (TASIT). A resampling procedure was employed to balance differences in samples size.** ***Results:*** **All clinical groups (DEL; DEL_SCZ; and SCZ) showed worse performance on TASIT than HCs, except in *Sincere* scale. No differences between-clinical groups were found, except for *Simple Sarcasm, Paradoxical Sarcasm* and *Enriched Sarcasm* scales.** ***Conclusions:*** **SC was impaired in individuals with 22q11.2DS regardless of psychotic symptomatology, similarly to people with SCZ. Therefore, SC deficits may represent potential endophenotypes of SCZ contributing to the vulnerability to psychosis.**

Key words: 22q11.2 deletion syndrome (22q11.2DS)/schizophrenia/psychosis/social cognition/theory of mind/social inference/neurocognition/Italian Network for Research on Psychoses

Introduction

22q11.2 Deletion Syndrome (22q11DS) represents the most common multisystemic syndrome with a chromosomal Copy Number Variation (CNV) as its etiologic factor; its incidence is 1:4000 new births, ranging from 1:3000 to 1:6000 according to literature.[1,2] It is caused by an autosomal dominant microdeletion at the 11.2 strand on the long arm (q) of chromosome 22, which is the most frequent interstitial deletion known in humans.[3] The syndrome is caused by a hemizygotic deletion of 1.5 to 3 megabases of DNA, involving about 40 coding genes. Despite its 100% penetrance, 22q11DS shows a large phenotypic variability both concerning the type and the severity of its clinical features which result from a common neurodevelopmental defect affecting neural crest cells.[4] In addition to several congenital defects involving different biological systems and organs, 22q11DS results in intellectual and learning disabilities, and other neuropsychiatric disorders.[5] In particular, a significant proportion of behavioral disorders during the developmental age[3] and

an increased incidence of mental disorders[6] have been observed in subjects with 22q11.2DS compared to the general population. The risk of 22q11.2DS for developing a psychotic illness during the lifespan, including schizophrenia (SCZ) and schizoaffective disorder, varies across various studies from 23% to 43%.[7,8] For this reason, this microdeletion represents one of the most important genetic risk factors for SCZ.[9] 22q11DS is a valuable, simplified biological model for studying neuropsychiatric disorders.[10] Such an approach aims at proposing a contribution to the study of factors likely involved in the etiopathogenesis of psychosis by investigating influences between the neurobiological underpinnings and environmental factors with a prominent role in idiopathic schizophrenia.[11] The neurocognitive profile of 22q11DS varies both across individuals and within the same individual during his/her lifespan.[12] Patients display psychomotor retardation and learning disabilities, in addition to impairments of visual-spatial processing, mathematical reasoning, working memory, and other executive functions.[13] A borderline cognitive level (IQ from 70 to 84) and a moderate intellectual disability have been reported in one-third of people with 22q11DS.[14] In these people, interpersonal difficulties, impulsiveness, introversion, and autistic spectrum features have been described.[15,16] Social Cognition (SC) consists of a large set of cognitive functions aimed at social inference and other's mental state representation.[17,18] It represents a complex net of cognitive processes required to correctly analyze and interpret information about social interactions, so to develop appropriate interpersonal abilities guiding social interactions and behaviors. SC consists of different cognitive domains including Theory of Mind (ToM), which is specifically aimed at other's mental state representation, so to guess people's intentions and behaviors.[19] Further SC domains are intended for correct inference of societal rules and social roles, for interpretation of interpersonal interactions, and for emotional content recognition in other people. SC was impaired in 22q11.2DS,[20] appearing particularly related to negative symptoms,[21] as well as in SCZ,[22,23] involving poor insight[24] and reduced social functioning.[25] In particular, significant evidence about Social Cognition deficits in 22q11.2DS compared to other idiopathic neuropsychiatric conditions, even once corrected for intellectual abilities, has been reported.[26] Social cognitive difficulties in 22q11.2DS have been studied from a neuroimaging point of view as well.[27]

SC impairments have been related to the psychopathological core of schizophrenia more than positive, negative, and disorganization symptoms.[28,29] Moreover, ToM proved to be similarly impaired in both chronic and first-episode psychosis patients.[30,31] An intermediate deficit was found in people at clinical high risk (CHR) and high genetic risk for psychosis compared to patients with psychosis and healthy controls (HCs).[24] Hence, common core social disabilities were postulated for both patients with an established psychosis and people at CHR or genetic risk for psychosis.[32] Therefore, 22q11.2DS represents a reliable biological model to study impaired SC. Executive functions and general cognitive abilities affect patients' SC abilities[33]; hence, individuals with global intellectual disability appear to have impaired SC. Similarly, SC performance results affected by neurocognition in CHR individuals,[34] like those with 22q11.2DS.

The aim of this study was to investigate Social Cognition (SC) impairments in a sample of adults with 22q11.2DS. We compared performances in a Social Perception and Theory of Mind (ToM) task between three clinical groups (the first consisting of individuals with 22q11.2DS and psychosis, the second of people with idiopathic schizophrenia, and the third of individuals with 22q11.2DS without psychotic illness) and a healthy control group. We expected to observe significant differences in ToM impairments between recruited groups, regardless of their cognitive level. More precisely, we hypothesized that people at high genetic risk for psychosis would also present social inference ability deficits, that worsen with psychotic onset.

Methods

Our sample consisted of 1730 individuals, aged between 16 and 66 years, divided in four groups: 22q11.2DS patients with diagnosis of psychosis (DEL_SCZ, N = 19); patients with SCZ without 22q11.2DS (SCZ, N = 887); 22q11.2DS patients with no diagnosis of psychotic disorder (DEL, N = 44); HCs with typical development (HCs, N = 780). Patients with schizophrenia were selected from a larger sample of 921 patients with psychosis to address missing values. Data for SCZ and HC groups were derived from the Italian Network for Research on Psychoses (NIRP), a multicenter study conducted in 26 Italian Universities involving different Departments of Psychiatry and Mental Healthcare Units, among which our Psychotic Disorders Outpatient Clinic.[29,35,36] This study aimed to identify factors affecting real-life functioning of patients with schizophrenia.[37] 22q11.2DS individuals were consecutively enrolled at the Department of Human Neuroscience, Policlinico Umberto I, Sapienza University of Rome, at a specialized Outpatient Clinic for 22q11.2DS from 2014 to 2018. Each participant signed free, informed consent. The study adopted the Principles of Human Rights, as issued by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964 and subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, in October 2013. The research protocol has been reviewed and approved by the Ethics Committee of the Umberto I University Hospital, Rome, Italy. All data were anonymized. Patient eligibility and diagnosis of psychotic disorder were based on the Structured Clinical Interview for DSM-IV Axis I Disorders / Patient Edition

(SCID-I /P),[38] with the aim to investigate the presence of other previous or current psychiatric symptomatology that would meet criteria for a DSM-5 diagnosis. Genetic diagnosis was ascertained through Fluorescent *In Situ* Hybridization (FISH).

The present study especially focused on the analysis of social inference abilities in the recruited clinical samples: with that aim, we employed The Awareness of Social Inference Test (TASIT)[39] which is a computerized task involving social perception and requiring the identification of thoughts, feelings, and characters' intentions in the frame of video vignettes. It focuses specifically on how participants identify white lies and sarcasm. It consists of 16 vignettes lasting about 15–60 seconds and representing interactions in which individuals tell lies or use sarcasm. At the end of the vision of each vignette, participants were asked to answer questions concerning the scenes, i.e., what someone is doing to another one? What someone is trying to say to another one? What someone is truly thinking about? What someone is truly feeling? TASIT score is calculated on seven scales organized in three sections: *emotion recognition* (positive emotions, PE; negative emotions, NE; sincere, SI); *social inference-minimal* (simple sarcasm, SS; paradoxical sarcasm, PS); *social inference-enriched* (lie, LI; enriched sarcasm, ES). TASIT has been previously employed in brain-injured patients and both in CHR for psychosis people and in chronic patients with psychosis, showing acceptable reliability.[39,40]

We assessed key cognitive domains through The MATRICS Consensus Cognitive Battery (MCCB) which measures clinical outcomes and treatment effectiveness as regards cognitive improvement in schizophrenia and related disorders.[41,42] It consists of 10 subtest, evaluating 7 cognitive domain: Speed of Processing (*Brief Assessment of Cognition in Schizophrenia Symbol Coding; Category Fluency: Animal Naming; Trail Making: Part A*); Attention/Vigilance (*Continuous Performance Test—Identical Pairs*); Working Memory (*Wechsler Memory Scale: Spatial Span; Letter-Number Span*); Verbal Learning (*Hopkins Verbal Learning Test—Revised*); Visual Learning (*Brief Visuospatial Memory Test—Revised*); Reasoning and Problem Solving (*Neuropsychological Assessment Battery: Mazes*); Social Cognition domain (*Mayer-Salovey-Caruso Emotional Intelligence Test*). We employed a MCCB Composite score as an indicator of cognitive level, consisting of the weighted average of battery subtest, except for the Social Cognition domain, according to the rationale of the study,[43] and except for the Attention/Vigilance domain, because most of 22q11 subjects were not able to complete it. Although the MCCB battery differs from IQ in describing the general cognition, we employed this tool because of its well-known effectiveness in assessing cognitive domains in schizophrenia.[44] The MCCB composite score was obtained calculating the remaining subtest mean *z*-scores compared to the mean of the normative sample employed by the Italian Network for Research on Psychoses.[44] For all SCZ patients, symptomatology was assessed with the Positive And Negative Syndrome Scale (PANSS).[45]

Statistical Analysis

The χ^2 test was employed to test differences in sex frequencies among groups. Differences in mean age, years of education, MCCB Composite score, PANSS scores, were analyzed through ANalysis Of VAriance (ANOVA). Since we were dealing with unbalanced samples because of the small size of the two subgroups with the rare syndrome, we proceeded to cross-validate the General Linear Model. Having samples of different sizes implies that the variance within the groups is different for the subgroups, the error variance is reduced by the square of the number of tests/subjects, and this problem would not be controlled proceeding with the bootstrap (resampling of the whole sample).[46,47] A MANCOVA model was applied on all data (Complete Model) to estimate the relationship between performance on the TASIT test and the four groups previously described, adjusted for sex, age, and MCCB Composite score. The HC group was considered as reference. Resampling was carried out choosing from large-sample groups (SCZ $n = 887$; HCs $n = 780$) random samples of similar size to that of the smaller groups for whom all data were used (DEL_SCZ $n = 19$; DEL $n = 44$) (Supplementary table 1S). Random sampling was implemented through the SPSS options in Data menu (select cases). We reported Beta coefficients in resampling as 95%CIs estimated by percentile (p95% CI). Beta coefficients were considered significant if p95% CI would not include 0. Comparisons between 95% CIs and p95% CIs were used to assess the Complete Model on which pairwise comparisons were calculated. Statistical significance was set at $P < .05$ for all analyses; however, Bonferroni's correction was applied appropriately to address multiple testing. We used the SPSS 25.0 version (Statistical Package for the Social Sciences, IBM Co., 2017) for all statistical analyses.

Results

Socio-demographic and clinical characteristics of the sample are presented in table 1.

The four groups significantly differed in gender composition ($\chi^2 = 81.680$; $P < .001$). More males were found in SCZ groups than among HCs. DEL groups did not differ in gender composition with respect to other groups.

A significant difference among groups was observed for age ($F_{3,1732} = 38.223$; $P < .001$). *Posthoc* analyses showed that both DEL and DEL_SCZ subjects were significantly younger than HCs and SCZ ($P < .001$). No differences were observed between these groups in mean age.

Table 1. Demographic and Clinical Characteristics of the Sample

	DEL_SCZ (N = 19)	DEL (N = 44)	SCZ (N = 887)	HC (N = 780)	TEST	P
GENDER					χ^2	
Male	15 (84.2%)	29 (65.9%)	616 (69.4%)	378 (48.5%)	81.680	<.001
Female	3 (15.8%)	15 (34.1%)	271 (30.6%)	402 (51.5%)		
					F	
AGE	26.6 ± 7.3	23.8 ± 6.6	40.0 ± 10.7	40.6 ± 12.5	38.223	<.001
MCCB Comp*	–1.44 ± 0.67	–0.97 ± 0.81	–1.23 ± 0.89	0.08 ± 0.70	379.854	<.001
PANSS						
Positive	18.1 ± 5.1	10.1 ± 3.2	15.9 ± 6.6		14.96	<.001
Negative	20.5 ± 5.2	12.2 ± 3.8	21.8 ± 8.4		23.058	<.001
General	42.7 ± 8.6	29.9 ± 7.3	37.1 ± 11.5		9.256	<.001
Total	81.3 ± 15.8	52.3 ± 12.6	74.8 ± 22.6		18.865	<.001

Note: * z-scores. Descriptive measures and group comparisons. For categorical variable (Gender) N size and (%) are shown for each group. For continuous variables (Age; MCCB Composite; PANSS) mean ± standard deviations are shown for each group. DEL, 22q11.2DS group without schizophrenia; DEL_SCZ, 22q11.2DS and schizophrenia group; HCs, healthy controls; SCZ, schizophrenia group.

The four groups showed a significant difference in years of education ($F_{3,1732}$ = 18.140; P < .001). However, posthoc comparisons found that only SCZ group had less years of education respect to HC (P < .001.)

MCCB Composite score was significantly different among groups ($F_{3,1732}$ = 379.854; P < .001). HCs scored higher than each clinical group (P < .001), while the three clinical groups did not differ at MCCB performance.

The three clinical groups differed in psychopathological symptoms severity, as shown by PANSS scores (table 1). As expected, *posthoc* tests showed significant less Positive (P < .001), Negative (P = .002), General (P < .001), and Total scores (P < .001) symptoms in the DEL group compared to DEL_SCZ and same results were observed for DEL respect to SCZ group (P < .001; P < .001; P < .001 and P = .001 for both group comparisons and for each PANSS scale score, respectively). The two psychotic groups did not differ on any PANSS score.

Intergroup Differences on TASIT Scales

A group effect emerged in multivariate covariance analysis (Roy's largest root $_{(7,1716)}$ = 0.143; P < .001). The univariate test analysis for subject effects showed that all seven dependent variables were significant (P < .001), except for the SI variable. The greater differences, considering the Eta index (η), were for paradoxical sarcasm (η = 0.400), simple sarcasm (η = 0.397), enriched sarcasm (η = 0.389), and negative emotions (η = 0.369) (Supplementary table 2S). DEL, DEL_SCZ, and SCZ scored lower than HCs on positive emotions, paradoxical sarcasm, lie, and enriched sarcasm, as shown by beta coefficients. Only the SCZ groups (i.e., not DEL) showed significant worst performance respect to HCs on negative emotions and simple sarcasm. No significant differences emerged among groups for the sincere variable (table 2).

Re-sampling

Group effects emerged in multivariate covariance analysis for all thirty sub-samples (P < .001); MCCB Composite effects also emerged for all sub-samples (P < .001), while both age and gender variables did not show significant differences (Supplementary table 3S). The last column of table 3 shows the 95% pCIs of the 30 Betas of the resampled subsample, calculated with the percentile method. Resampling is consistent with the Complete Model (both for multivariate and univariate analyses).

Group Comparisons in the Complete Model

Pairwise comparisons of the positive emotions variable showed significant differences between HCs and each clinical group (P < .001), while clinical groups did not differ from one another, except for the DEL_SCZ *vs*. SCZ comparison (P = .048), where the DEL_SCZ group scoring lower than SCZ (figure 1). Comparisons for the negative emotions variable between HCs *vs.* SCZ (P < .001) and HCs *vs*. DEL_SCZ (P = .004) showed significant differences, while the DEL *vs.* HCs and between-clinical groups comparisons did not produce statistical differences, and so did comparisons for the sincere variable. HCs differed from all clinical groups on simple sarcasm, paradoxical sarcasm, lie, and enriched sarcasm, except for the DEL *vs.* HCs comparison on the simple sarcasm variable (table 3 and figure 1). Comparisons between-clinical groups were significant for the simple sarcasm variable except for DEL-SCZ vs SCZ; DEL_SCZ *vs*. DEL, with the DEL_SCZ group scoring lower (P = .002); SCZ *vs.* DEL, with the SCZ group scoring lower (P < .001).

Concerning the paradoxical sarcasm variable, DEL_SCZ scored lower than SCZ (P = .020), while on the

Table 2. Complete Model Beta Values, Adjusted by Sex, MCCB and Age

Variable	Group	Beta	CI 95%	*P* value	Resampling pCI 95%
TASIT_PE					
	DEL_SCZ	–1.67	–2.6; –0.74	<.001	–2.46; –1.10
	SCZ	–0.76	–1.02; –0.52	<.001	–1.45; 0.13
	DEL	–1.06	–1.7; –0.4	.001	–1.79; –0.62
	HCs	ref			
TASIT_NE					
	DEL_SCZ	–1.78	–3.0; –0.54	.004	–2.70; –1.42
	SCZ	–1.22	–1.56; –0.87	<.001	–2.13; –0.60
	DEL	–0.56	–1.5; 0.29	.197	–1.44; –0.28
	HCs	ref			
TASIT_SI					
	DEL_SCZ	–0.78	–2.7; 1.31	.435	–3.00; 0.50
	SCZ	–0.13	–0.65; 0.42	.636	–2.69; 0.62
	DEL	–1.07	–2.4; 0.29	.121	–3.11; –0.40
	HCs	ref			
TASIT_SS					
	DEL_SCZ	–4.47	–6.24; –2.39	<.001	–6.56; –2.08
	SCZ	–3.44	–3.89; –2.86	<.001	–5.01; –1.70
	DEL	–1.10	–2.41; 0.18	.092	–3.03; 1.15
	HCs	ref			
TASIT_PS					
	DEL_SCZ	–5.62	–6.36; –2.59	<.001	–8.41; –4.14
	SCZ	–3.23	–3.95; –2.92	<.001	–5.49; –1.52
	DEL	–4.42	–2.40; 0.2	<.001	–6.89; –2.88
	HCs	ref			
TASIT_LI					
	DEL_SCZ	–2.95	–5.52; –0.38	.024	–5.31; –0.72
	SCZ	–2.86	–3.56; –2.15	<.001	–5.14; –0.41
	DEL	–4.60	–6.37; –2.82	<.001	–6.66; –2.46
	HCs	ref			
TASIT_SE					
	DEL_SCZ	–5.76	–8.37; –3.14	<.001	–8.10; –3.17
	SCZ	–4.26	–4.98; –3.55	<.001	–6.82; –1.87
	DEL	–2.40	–4.22; –0.58	.010	–4.33; –0.02
	HCs	ref			

Note: Resampling Confidence Interval have been calculated with percentile method. CI, confidence interval; DEL, 22q11.2DS group; DEL_SCZ, 22q11.2DS and schizophrenia group; HCs, healthy controls; SCZ, schizophrenia group; TASIT_PE, positive emotions; TASIT_NE, negative emotions; TASIT_SI, sincere; TASIT_SS, simple sarcasm; TASIT_PS, paradoxical sarcasm; TASIT_LI, lie; TASIT_SE, enriched sarcasm.

enriched sarcasm scale, DEL_SCZ scored lower than DEL (P = .027); in clinical intergroup comparisons, DEL_SCZ scored lowest, SCZ intermediate, and DEL highest.

Comparisons of the lie and enriched sarcasm variables showed significant differences between HCs and each clinical group, while clinical groups did not differ from one another (table 3, figure 1).

Applying Bonferroni's correction only results for $p \leq 0.004$ were considered statistically significant.

Discussion

This study aimed at investigating SC in a sample of subjects with 22q11.2DS at high clinical and genetic risk for psychoses compared to patients with SCZ and HCs. We studied this rare genetic syndrome which represents the best-known high-risk condition for psychosis onset to shed light on the neurobiological underpinnings of SCZ by investigating the potential SC deficits in 22q11.2DS and exploring whether social inference would worsen with psychosis. With this aim, we studied a large sample derived from a previous multicenter study of the Italian Network for Research for Psychoses.

The core result of the study is that people with 22q11.2DS show SC performances similar to those of patients with SCZ, regardless of the presence of psychotic symptoms. Overall, we did not find significant differences among clinical groups on SC performance, while HCs performed significantly better both on simple emotion recognition and in complex social inference tasks. These findings suggest that individuals with 22q11.2DS display SC deficits time before psychotic onset. To our knowledge, this is the first study to report SC deficits in adults

Table 3. Complete Model Pairwise Comparisons

	Difference of Means	St Err	*P*-value	CI 95%	
				Lower limit	**Upper limit**
TASIT_PE					
DelSCZ vs SCZ	–0.896*	0.458	*.048*	–1.794	–0.001
DelSCZ vs DEL	–0.606	0.538	*.260*	–1.662	0.450
DelSCZ vs HCs	–1.668*	0.474	***.000***	–2.598	–0.739
SCZ vs DEL	0.290	0.312	*.353*	–0.322	0.902
SCZ vs HCs	–0.772*	0.130	***.000***	–1.027	–0.517
DEL vs HCs	–1.062*	0.329	***.001***	–1.706	–0.417
TASIT_NE					
DelSCZ vs SCZ	–0.558	0.603	*.355*	–1.742	0.625
DelSCZ vs DEL	–1.220	0.710	*.086*	–2.612	0.172
DelSCZ vs HCs	–1.779*	0.625	***.004***	–3.005	–0.554
SCZ vs DEL	–0.662	0.412	*.108*	–1.469	0.146
SCZ vs HCs	–1.221*	0.171	***.000***	–1.557	–0.886
DEL vs HCs	–0.559	0.433	*.197*	–1.409	0.291
TASIT_SI					
DelSCZ vs SCZ	–0.649	0.962	*.50*	–2.535	1.238
DelSCZ vs DEL	0.295	1.131	*.794*	–1.924	2.514
DelSCZ vs HCs	–0.778	0.996	*.435*	–2.731	1.176
SCZ vs DEL	0.944	0.656	*.150*	–0.343	2.230
SCZ vs HCs	–0.129	0.273	*.636*	–0.664	0.406
DEL vs HCs	–1.073	0.691	*.121*	–2.427	0.282
TASIT_SS					
DelSCZ vs SCZ	–1.038	0.926	*.262*	–2.855	0.778
DelSCZ vs DEL	–3.375*	1.090	***.002***	–5.512	–1.237
DelSCZ vs HCs	–4.474*	0.959	***.000***	–6.356	–2.592
SCZ vs DEL	2.336*	0.632	***.000***	–3.576	–1.097
SCZ vs HCs	–3.436*	0.263	***.000***	–3.951	–2.920
DEL vs HCs	–1.100	0.665	*.099*	–2.404	0.205
TASIT_PS					
DelSCZ vs SCZ	–2.385*	1.023	*.020*	–4.392	–0.378
DelSCZ vs DEL	–1.197	1.204	*.320*	–3.557	1.164
DelSCZ vs HCs	–5.617*	1.060	***.000***	–7.695	–3.538
SCZ vs DEL	1.188	0.698	*.089*	–0.181	2.557
SCZ vs HCs	–3.232*	0.290	***.000***	–3.801	–2.662
DEL vs HCs	–4.420*	0.735	***.000***	–5.861	–2.979
TASIT_LI					
DelSCZ vs SCZ	–0.090	1.264	*.943*	–2.569	2.388
DelSCZ vs DEL	1.657	1.487	*.265*	–1.259	4.573
DelSCZ vs HCs	–2.949*	1.309	*.024*	–5.516	–0.381
SCZ vs DEL	1.747*	0.862	*.043*	0.056	3.438
SCZ vs HCs	–2.859*	0.359	***.000***	–3.562	–2.155
DEL vs HCs	–4.605*	0.908	***.000***	–6.386	–2.825
TASIT_SE					
DelSCZ vs SCZ	–1.492	1.289	*.247*	–4.020	1.037
DelSCZ vs DEL	–3.355*	1.516	*.027*	–6.330	–0.381
DelSCZ vs HCs	–5.756*	1.335	***.000***	–8.375	–3.137
SCZ vs DEL	–1.864*	0.879	*.034*	–3.589	–0.139
SCZ vs HCs	–4.265*	0.366	***.000***	–4.982	–3.547
DEL vs HCs	–2.401*	0.926	*.010*	–4.216	–0.585

* Difference of mean statistically significant ($P < .05$); significant *P*-values in **bold**. CI, confidence interval; St. Err., standard error; TASIT scales: TASIT_PE, positive emotions; TASIT_NE, negative emotions; TASIT_SI, sincere; TASIT_SS, simple sarcasm; TASIT_PS, paradoxical sarcasm; TASIT_LI, lie; TASIT_SE, enriched sarcasm; Groups: DEL, 22q11.2DS group; DEL_SCZ, 22q11.2DS and schizophrenia group; HCs, healthy controls; SCZ, schizophrenia group.

with 22q11.2DS compared to such a considerable number of patients with SCZ without a known genetic condition. We found that the DEL_SCZ group did not significantly differ from the SCZ group regarding global psychotic symptoms, even if the DEL_SCZ group displayed more accentuated positive symptoms compared to the SCZ group. It should be noted that our analysis considered differences in cognitive level among groups, employing the MCCB Composite score as a covariate, so to avoid the potential influence on Social Cognition performance.

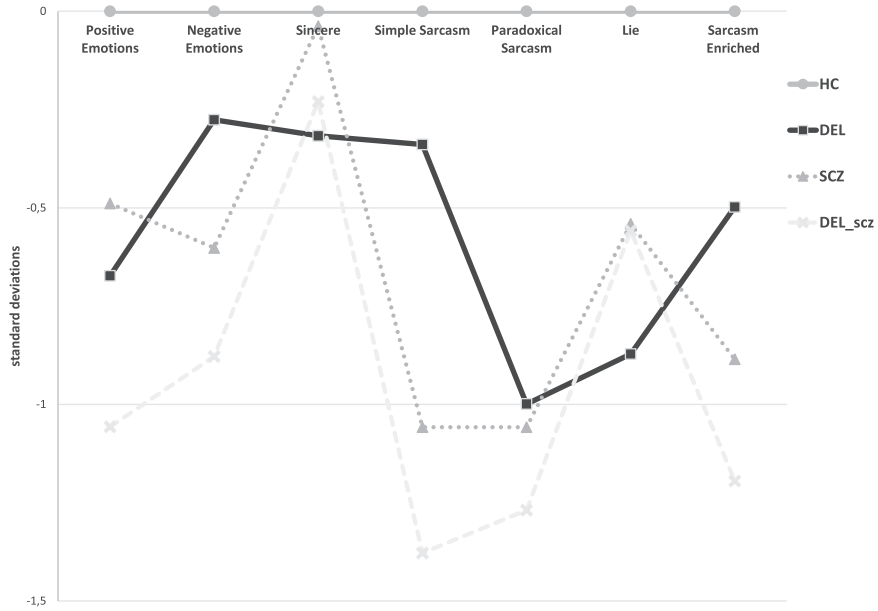

Fig. 1. Profile of the performances on the seven TASIT scales for each group. All variables were standardized with respect to the HC group, considered as the normative sample represented as the 0 line. Values are expressed in standard deviation units with respect to the normative sample (*z*-scores). Negative values indicate poorer performance with respect to the normative sample.

Concerning the more complex inference abilities as described by the simple sarcasm scale of the social inference-minimal domain we may suppose that a tight association between psychotic illness and sarcasm recognition inefficiency exists, which is similar to that of patients with SCZ and of people with 22q11.2DS; psychotic illness appears to worsen their ability in sarcasm recognition compared to people carrying this genetic condition without psychotic symptoms. The paradoxical sarcasm scale showed a different trend, with 22q11DS individuals being more impaired with respect to SCZ. We may presume a significant effect of 22q11.2DS on more complex social inference abilities. Moreover, in the social inference-enriched section, results of both lie and enriched sarcasm scales show that people with 22q11.2DS and individuals with schizophrenia without known genetic condition have similar impairments in sarcasm recognition abilities, compared to healthy controls. However, psychosis may further impair sarcasm recognition.

Notably, our findings confirm the existence of ToM deficits in SCZ[48] and show that people with 22q11.2DS display similar SC deficits in social contexts involving complex interactions with sarcastic and ironic communications. In such situations, misinterpretation and attributional bias would likely significantly impair social perception. Interestingly, SC impairments in 22q11.2DS may be present long before a psychotic onset and basic ToM abilities in people with 22q11.2DS do not appear to be further impaired by psychotic symptoms; however, our findings suggest that psychotic symptoms likely worsen more complex ToM processes like sarcasm recognition. Individuals with 22q11.2DS without psychotic symptoms, but at high genetic risk for its onset, show social inference deficits like individuals with schizophrenia, suggesting an "all or nothing" mechanism of SC processes. Social inference deficits could be related in a substantial proportion to neurodevelopmental factors and may determine vulnerability to psychosis.

Regarding a more basic social inference level, our findings suggest that people with 22q11.2DS share similar impairments in decoding processes of basic emotional patterns as those observed in individuals with SCZ: on the positive emotions scale, all clinical groups showed significant impairments compared to HCs, while on the negative emotions scale, only individuals with active psychosis, who often display ideas of reference and persecution, and could be more prone to misinterpret simple negative emotions, showed significant impairments on negative emotions recognition compared to HCs. As already evidenced in the frame of the syndrome, we presume that higher peripheral decoding impairments may worsen performances of people with 22q11.2DS and psychosis in positive emotion recognition, compared both to SCZ and HCs. Positive emotions seem to require more complex decoding abilities in comparison to negative ones, which appeared to be correctly detected by individuals with 22q11.2DS. Our study suggests a common ability of people with 22q11.2DS and individuals with SCZ to correctly interpret authentic communications, trusting simple and direct statements, as shown by the absence of significant differences between-clinical groups on the sincere scale.

Several studies have considered social ability impairment as nuclear in psychotic illness, even more than

productive, negative, or disorganized symptoms.[4,8,48,49] Different models were used to explain SC dysfunctions underlying psychotic symptoms.[50–52] Individuals with SC deficits would be prone to attribute abnormal, hostile, and persecutory intentions to interlocutors, consequently influencing their own behaviors and emotions. These considerations suggest that SC deficits, according to Gottesman and Gould's original conception,[20] could represent a reliable endophenotype of vulnerability to psychosis, useful to define a stable and dimensional element meant to differentiate clinical groups with respect to different levels of risk.[53]

Social inference abilities in 22q11.2DS have been previously related to executive functions,[54,55] perceptual processes,[56] and general cognitive functioning.[12,57,58] According to literature, SC in 22q11.2DS has been mainly evaluated by tools investigating static visual perception,[59] emotion recognition,[60] executive functions,[55,61] and related neurofunctional underpinnings.[62,63] In the current study, we employed the TASIT, which is a dynamic tool representing everyday-life situations and usual interpersonal interactions by means of specific acting performances, in order to evaluate social inference abilities. We focused on the social-cognitive component of ToM, according to the evidence of its distinction from a social-perceptual one in the frame of genetic neurodevelopmental disorders.[64] Moreover, impaired facial expression perception has been previously suggested as a reliable endophenotype of psychotic symptoms in 22q11.2DS, rather than explicit recognition of the emotion expressed[56]; however there is lack of evidence for such findings concerning individuals with SCZ without known genetic background. Although ToM and mentalizing abilities have been previously investigated in 22q11.2DS even by means of TASIT,[65] social cognitive deficits and developmental trajectories have been mainly observed with respect to HCs.[66] The present study investigated social inference abilities in 22q11.2DS compared to a large sample of patients with SCZ without considering static perceptual processes. Such comparison appears to be fundamental for shedding light over common neurocognitive impairments in a genetic condition at risk for psychosis, such as 22q11.2DS, and full-blown SCZ. Similar SC impairments between these clinical features may be related to overlapping neurodevelopmental defects. These might have in turn determined similar impairments in basic neurobiological substrates that are needed for effective social inference abilities. In particular, social perception impairments and tendency to social interaction misinterpretation may lead to an increased proneness to attributional bias and to a higher risk for psychotic onset. Finally, autism spectrum disorders and the related symptomatology are present in a significant proportion of people with 22q11.2DS, likely influencing social cognition abilities.[67] However, autistic features in 22q11.2DS did not result in direct increase in the risk of developing psychotic disorders.[10] For this reason, we decided to directly focus our study on SC impairments in 22q11.2DS, without addressing autistic spectrum features.

The main limitation of this study is the imbalanced sample sizes of the four groups. 22q11.2DS is a rare syndrome with a low incidence, making it hard to recruit an adequately sized sample with this microdeletion. However, to avoid any potential sample size influence, we employed a statistical methodology that enabled us to perform reliable analyses. Another limitation is the evidence of delayed intellectual maturation in the 22q11.2DS groups, which likely influenced social inference and social perception performances. To address these drawbacks, we considered a MCCB Composite score as a covariate of our analysis, so to avoid any potential influence of the general cognitive level of recruited individuals. Another limitation of the study is that we did not specifically look at the relationships between Social Inference dysfunctions and deficits in executive and general cognitive profiles of the recruited patients: however, we expressly focused on Social Cognition with the aim of defining whether its deficits might be associated to an increased vulnerability to psychosis.

Conclusions

In conclusion, Social Cognition resulted impaired in individuals with the 22q11.2 Deletion Syndrome similarly to people with schizophrenia without known genetic condition. More significantly, social inference was impaired regardless of the presence of psychotic symptoms, slightly worsening only in higher social perception abilities for people with 22q11.2DS and a psychotic illness. Therefore, deficits in social cognitive process in 22q11.2DS could be considered as potential endophenotypes of psychotic illness, useful to differentiate clinical groups with respect to their different levels of risks. These findings emphasize the need for cognitive remediation techniques, social skills training, and social interventions for individuals at high clinical and genetic risk for psychosis as those with 22q11.2DS, thus improving their global functioning and their interpersonal abilities, so to prevent or postpone psychotic onset. Further longitudinal studies should investigate whether people with worse ToM deficits are at higher risk of developing a psychotic illness.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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