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RESEARCH ARTICLE

Social cognition and real-life functioning in patient samples with 22q11.2 deletion syndrome with or without psychosis, compared to a large sample of patients with schizophrenia only and healthy controls

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Abstract

Patients with the 22q11.2 deletion syndrome (DS) show an increased risk of developing a psychotic illness lifetime. 22q11.2DS may represent a reliable model for studying the neurobiological underpinnings of schizophrenia. The study of social inference abilities in a genetic condition at high risk for psychosis, like 22q11.2DS, may shed light on the relationships between neurocognitive processes and patients' daily general functioning. The study sample consisted of 1736 participants, divided into four groups: 22q11.2DS patients with diagnosis of psychotic disorder (DEL SCZ, $N = 20$); 22q11.2DS subjects with no diagnosis of psychosis (DEL, $N = 43$); patients diagnosed with schizophrenia without 22q11.2DS (SCZ, $N = 893$); and healthy controls (HC, $N = 780$). Social cognition was assessed through The Awareness of Social Inference Test (TASIT) and general functioning through the Specific Levels of Functioning (SLoF) scale. We analysed data through regression analysis. The SCZ and DEL groups had similar levels of global functioning; they both had significantly lower SLoF Total scores than HC ($p < .001$); the DEL SCZ group showed

significantly lower scores compared to the other groups (SCZ, $p = .004$; DEL, $p = .003$; HC, $p < .001$). A significant deficit in social cognition was observed in the three clinical groups. In the DEL SCZ and SCZ groups, TASIT scores significantly predicted global functioning ($p < .05$). Our findings of social cognition deficit in psychosis-prone patients point to the possible future adoption of rehabilitation programmes, like Social Skills Training and Cognitive Remediation, during premorbid stages of psychosis.

KEYWORDS

22q11 deletion syndrome, functional outcome, psychosis, schizophrenia, social cognition

INTRODUCTION

Schizophrenia is currently one of the main causes of disability worldwide. Patients display severe impairments in the domains of independent living, productive activities, and social abilities (Harvey & Strassnig, 2012). Presently, functional outcomes of patients with schizophrenia are considered among the main targets of treatment (Galderisi et al., 2014). In fact, to obtain recovery in schizophrenia, the focus is not only on symptom management, but also on regaining social and occupational functioning (Bucci et al., 2018). The clinical assistance of patients with psychosis entails rehabilitation programmes such as social skills training and cognitive remediation and aims to achieve independent living. To provide proper treatment for schizophrenia, there is need to deepen the knowledge of factors contributing to functional impairments. Neurocognitive deficits (Leifker et al., 2011), negative symptoms (Galderisi et al., 2013), and depression (Rieckmann et al., 2005) have been described as the main factors involving poor functional outcomes in patients with schizophrenia. Several studies found that neurocognitive deficit could be a better predictor of functional outcome in schizophrenia than other features of the illness (Fett et al., 2011). However, there is mounting evidence that not only neurocognitive functions, such as working memory, attention, and other executive functions are related to everyday functioning in schizophrenia, but also Social Cognition (SC) impairments are increasingly associated with functional outcome (Fett et al., 2011). Some studies suggested several roles for SC in determining patient functioning (Kee et al., 2003; Meyer & Kurtz, 2009; Pinkham & Penn, 2006). It has been proposed that SC could represent a mediator between neurocognition and specific outcomes (Meyer & Kurtz, 2009); moreover, SC abilities seem to represent reliable and independent predictors, accounting for variance not explained by other variables (Pinkham & Penn, 2006) and for correlations between SC impairments and poor social and occupational functioning in patients with schizophrenia (Kee et al., 2003).

To our knowledge, few studies investigated real-life functioning domain impairments in a population at high genetic risk of developing psychosis, like patients with 22q11.2 microdeletion, an autosomal dominant microdeletion at the 11.2 strand on the long arm (q) of chromosome 22. This microdeletion is the most common known rare Copy Number Variation, causing 22q11.2 Deletion Syndrome (22q11.2DS), which is a multi-system syndrome with an incidence ranging from 1:3000 to 1:6000 of new births (Olsen et al., 2018). The hemizygotic 22q11.2 microdeletion involves about 40 coding genes displaying a large phenotypic expression that regards different clinical conditions deriving from a common neurodevelopmental defect which affects the neural crest. Congenital heart defects, thymus hypoplasia with primary immunodeficiency and palatal defects have been observed in the frame of the syndrome (Ardinger & Ardinger, 2002). In addition to the evidence of delayed intellectual maturation, 22q11.2DS has been related to several neuropsychiatric and behavioural disorders. In particular, individuals with 22q11.2DS show an increased risk of developing a psychotic illness during their lifespan,

Significant Outcomes

- A similar deficit in global functioning between non-psychotic 22q11DS subjects and patients with idiopathic schizophrenia was observed.
- Results showed that both symptom severity and the extent of social cognition deficits were involved in the level of functioning of DEL SCZ patients.

Limitations

- 22q11DS groups had a small sample size.
- The present study had an observational design, while more accurate information on the predictive value of social cognition deficits on global functioning could be obtained through a longitudinal study.
- Comorbidity data were not available.

including schizophrenia and schizoaffective disorder, with rates ranging in various studies from 23% to 43% (Schneider et al., 2014). Psychotic symptoms in 22q11.2DS have been described as comparable to those of schizophrenia without a clear genetic aetiology; thus, this syndrome may represent a reliable model for studying the neurobiological underpinnings of schizophrenia and psychotic disorders (Bassett et al., 2003). 22q11.2DS renders the further investigation of the interactions between neurobiological defects and environmental factors feasible, in a frame of genetic risk of developing psychosis. Furthermore, this syndrome provides the opportunity to define the impact of specific neurodevelopmental defects on psychotic symptom development and patients' functional outcomes. For these reasons, research focused on the neurocognitive profile of 22q11.2DS, revealing significant variations both inter-individually and intra-individually across the lifespan (Morrison et al., 2020). A decline in neurocognition in 22q11.2DS has been associated with a significant risk for psychotic onset (Vorstman et al., 2015). In addition to learning disorders, intellectual disability, and executive function impairments, 22q11DS patients display social inference difficulties, with a SC impairment which is similar to that of schizophrenia (Milic et al., 2021). In both conditions, SC and Theory of Mind (ToM) deficits involve other's mental state and intentions representation, social inference disabilities, and difficulties in preventing others' behaviours (Bora & Pantelis, 2013; Lattanzi et al., 2018; Moberg et al., 2018; Rocca et al., 2016; Schneider, Schaer, et al., 2014; Weinberger et al., 2016). Even though general neurocognition has been previously related to SC processes, there is evidence that they are distinct constructs with different neurobiological underpinnings (Mehta et al., 2013). Indeed, SC has been described as a potential mediator between neurocognition and patients' general functioning (Sergi et al., 2006), thus representing a potential therapeutic target. Despite increasing interest in the study of 22q11.2DS, currently few data are available about patients' real-life functioning. Previous studies revealed that SC impairments as well as social functioning and social skill deficits impact real-life functioning of individuals with 22q11.2DS (Vangkilde et al., 2016). This syndrome involves significant difficulties in establishing long-term relationships or reaching economic autonomy and independence (Butcher et al., 2012). Patients' functional impairments are related to the severity of psychotic and anxiety symptoms and of cognitive deficits. Evidence is accumulating that higher impairments in social competence are associated with worse subclinical negative symptoms in 22q11DS (Milic et al., 2021). Social impairments were substantially independent from reduced intellectual functioning (Vangkilde et al., 2016). Social functioning gradually deteriorated during childhood and early adolescence in those individuals with 22q11.2DS who subsequently went on to develop schizophrenia (Yuen et al., 2013). Given that SC impairments have been related to overall functioning and recovery outcomes in patients with schizophrenia, investigating

social inference abilities in a genetic condition at high risk for psychosis, such as 22q11.2DS, may shed light on the interactions between neurocognitive processes and patients' everyday general functioning.

Our primary objective was to investigate SC of the four samples considered here, through The Awareness of Social Interference Test (TASIT). Our hypothesis was that patients with deletion and psychosis would show similar decreases in SC, independent from other cognitive domain dysfunctions. Secondary outcomes were to compare the four groups on (1) real-life functioning, assessed through the Specific Level of Functioning (SLoF) scale; (2) the impact of ToM (with TASIT as the proxy) on global functioning (SLoF). We hypothesised that the groups would differ on daily functioning and that this would be affected by SC impairment.

MATERIALS AND METHODS

Participants

The current study involved 1736 participants, aged 16–66 years, divided into four groups: 22q11.2DS patients with diagnosis of psychotic disorder (DEL SCZ, $N = 20$; 10 patients received a diagnosis of Schizophrenia, three Schizophreniform Disorder, and seven Psychotic Disorder Not Otherwise Specified); 22q11.2DS subjects with no diagnosis of psychosis (DEL, $N = 43$); patients diagnosed with Schizophrenia without 22q11.2DS (SCZ, $N = 893$); and Healthy Controls with typical development (HCs, $N = 780$). Both SCZ groups were on stable medication and not in an acute phase of the illness. 22q11DS participants underwent complete genetic investigation and the diagnosis was determined through Fluorescent *in situ* hybridisation or array-comparative genomic hybridisation. Individuals with multiple genetic abnormalities were excluded. Patients with an IQ score <50 (i.e., those with moderate or severe intellectual disability) were not included.

Inclusion and exclusion criteria for recruited groups

For the DEL group, the inclusion criteria are the presence of a 22q11.2 microdeletion and the exclusion criteria are a diagnosis of schizophrenia spectrum disorder or severe intellectual disability. For the DEL-SCZ group, the inclusion criteria are the presence of a 22q11.2 microdeletion and a diagnosis of schizophrenia spectrum disorder on stable medication in the last 8 weeks; the exclusion criteria are the presence of a severe intellectual disability and a history of admission or variation in prescription due to exacerbation in the previous 3 months. For the SCZ group, the inclusion criteria are a diagnosis of schizophrenia spectrum disorder on stable medication in the last 8 weeks; the exclusion criteria are the presence of genetic abnormalities, of severe intellectual disability or a history of admission or variation in prescription due to exacerbation in the previous 3 months. For the HCs group, the exclusion criteria are the presence of genetic abnormalities or psychiatric disorders.

Databases

Data for the SCZ and HC groups were derived from the Italian Network for Research on Psychoses, a multi-centre study involving 26 Departments of Psychiatry and Mental Healthcare Units of Italian Universities, among which our Psychotic Disorders Outpatient Clinic (Galderisi et al., 2014, 2020). This study was aimed at identifying factors affecting real-life functioning of patients with schizophrenia (Galderisi et al., 2018). 22q11.2DS individuals were consecutively enrolled at *omissis* the 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 *omissis*. All data were anonymised.

Assessments

Demographic and clinical data collected for all participants included age, years of education and sex; data regarding age at onset of psychosis, duration of illness (DoI) and type of antipsychotic treatment to which patients were exposed (i.e., no antipsychotics, first-generation antipsychotics, second-generation antipsychotics, or both) were collected only for groups of patients with psychosis. Intelligence Quotient data were available only for 22q11DS subjects, as they performed a Raven Standard Progressive Matrices test.

Diagnosis of psychotic disorder was based on the Structured Clinical Interview for DSM-IV Axis I Disorders/Patient Edition (SCID-I/P; First et al., 2016), which investigates the presence of previous or current psychiatric symptomatology that would meet the criteria for a DSM-5 diagnosis. Symptomatology was assessed in all groups, with the Positive And Negative Syndrome Scale (PANSS; Kay et al., 1987). The MATRICS Consensus Cognitive Battery (MCCB) is a psychometric tool intended to provide a relatively brief evaluation of key cognitive domains relevant to schizophrenia and related disorders. It measures clinical outcomes and treatment effectiveness as regards cognitive improvement in schizophrenia and related disorders (Kern et al., 2008; Nuechterlein et al., 2008). It consists of 10 subtests, evaluating seven cognitive domains: *Speed of Processing*; *Attention/Vigilance*; *Working Memory*; *Verbal Learning*; *Visual Learning*; *Reasoning and Problem Solving*; and *Social Cognition*. We employed a MCCB Composite score, consisting of the weighted average of battery subtests, except for the *Social Cognition* domain, according to the rationale of the present study, and except for the *Attention/Vigilance* domain, because most of the 22q11 deletion patients were not able to complete it. The MCCB Composite score was obtained calculating the remaining subtest mean z-scores compared to the mean of the normative sample of the Italian Network for Research on Psychoses. This parameter was obtained with the precise purpose of adjusting the results of Social Cognition analyses for any further potentially present cognitive dysfunction. SC was evaluated through The Awareness of Social Inference Test (TASIT; McDonald et al., 2006) which is a computerised task involving social perception and requiring the identification of thoughts, feelings, and characters' intentions in the context of video vignettes. We used the Italian version of the test, which showed similar psychometric properties to the original (Mucci et al., 2014). TASIT scores are calculated on seven scales, summed up in three sections: Positive Emotions and Negative Emotions compose *Emotion Recognition*; Sincere, Simple Sarcasm and Paradoxical Sarcasm constitute to *Minimal Social Inference*; Sarcasm Enriched and Lie form the section *Social Inference Enriched*. A TASIT total score has also been calculated. TASIT score has been standardised to $M = 50$ and $SD = 10$.

Participants' general functioning was assessed through the Specific Levels of Functioning scale (SLoF), a 43-item multidimensional behavioural interview, referring to the past week, which is administered to the caregiver of the patient (Mucci et al., 2014). SLoF assesses patient's functioning and independent living by investigating the following three domains (Schneider & Struening, 1983), each comprising two factors of the scale: *Self Maintenance*, including the subscales Physical Functioning and Personal Care Skills; *Social Functioning*, which evaluates both Interpersonal Relationships and Social Acceptability; *Community Living Skills*, in which Activities and Work Skills are considered. The scale assesses participants' current functioning and observable behaviour and does not include items relevant to psychiatric symptomatology or cognitive dysfunction. Scores on the instrument range from 43 to 215. The higher the Total score (SLoF Total score), the better the overall functioning of the patient.

Statistical analyses

Differences in continuous demographic and clinical variables were analysed through ANalysis Of VAriance. Homogeneity of variance was tested and if this assumption was violated Welch's statistic would be applied. For the variables examined only in DEL SCZ and SCZ groups, the *t*-test for independent samples was used. Bonferroni's correction was applied to *post-hoc* comparisons, but also the Games-Howell test was employed to address the violation of the homogeneity of variance assumption and to control for the difference in group size. Differences in categorical variables were investigated through Pearson's *chi*-square test.

A Multivariate ANalysis of COVAriance (MANCOVA) was conducted to assess group differences in TASIT performance. TASIT data were missing for nine SCZ patients and for six HC participants. Scores of the three TASIT subscales *Emotion Recognition*, *Minimal Social Inference*, *Social Inference Enriched*, plus the sum of them (i.e., TASIT Total score), were entered in the model as dependent variables. Group variables were considered as the fixed factor. Age and MCCB Composite Score were covariates. *Post-hoc* results were corrected with Bonferroni's correction for multiple comparisons. Differences in SLoF scores among groups were analysed employing a Multivariate ANalysis of VAriance (MANOVA). *Self-Maintenance, Social Functioning, Community Living Skills*, and SloF Total Score were considered as dependent variables. Bonferroni's and Games-Howell tests were applied to *post-hoc* comparisons.

A linear regression was employed to evaluate which variable determined the functioning level of participants in each group. SloF Total score was set as the outcome variable of the model. Several continuous variables were inserted as predictors in model, chosen according to literature, through a *stepwise* method, i.e., TASIT Total, PANSS Total, MCCB Composite, and Age. DoI was also considered as a predictor in SCZ groups. The Durbin-Watson test was used to control the validity of the statistics obtained; values of 1–3 represented cause for concern.

RESULTS

Sociodemographic and psychopathological variables

The four groups showed significant differences in the following variables (Table 1): Age; Years of Education; PANSS Positive Symptoms; PANSS Negative Symptoms; PANSS General Psychopathology; PANSS Total; and MCCB Composite score.

Post-hoc testing (Table 1) showed a significantly lower mean age in 22q11DS groups with respect to SCZ and HC.

Regarding Years of Education, the HC group received more education than SCZ, while no differences emerged between the 22q11DS groups and HCs.

Concerning PANSS scores, both DEL SCZ and SCZ groups showed significantly more severe PS compared to DEL and HC. Moreover, DEL was found to have a significant higher PANSS PS score compared to HC. Similar results were observed for Negative Symptoms: DEL SCZ and SCZ groups showed significantly higher scores on NS compared to DEL and HC, and the DEL group scored higher than HC. With respect to PANSS GP, DEL SCZ and SCZ groups scored higher than DEL and HC, but General Psychopathology symptoms were also more severe in the DEL SCZ compared to the SCZ, and the DEL groups compared to HC. PANSS Total score was significantly higher in DEL SCZ and SCZ groups compared to DEL and HC. Furthermore, 22q11DS patients without psychosis displayed higher PANSS Total scores compared to HCs.

As for cognitive abilities, the three clinical groups were found to perform significantly worse on the MCCB compared to HC ($p < .001$), with no significant differences among the three clinical groups.

When SCZ and DEL SCZ groups were compared for the age of the first psychotic episode, 22q11DS participants showed an earlier psychotic onset. The DoI was longer in the SCZ group. No significant

TABLE 1 Demographic and clinical variables with between-groups differences.

(a)							*Post hoc*				
Continuous variables	**DELSCZ *N*=20**	**SCZ *N*=893**	**DEL *N*=43**	**HC *N*=780**	***F***	***p***	**Group comparison**		**Mean difference**	**Standard error**	***p***
Age	26.5 ± 7.2	40.0 ± 10.7	23.8 ± 6.7	40.6 ± 12.5	38.206	<.001	DELSCZ	SCZ	−13.52[a]	2.59	<.001
								DEL	2.71	3.10	1.000
								HC	−14.07[a]	2.59	<.001
							SCZ	DEL	16.23[a]	1.79	<.001
								HC	−.55	.56	1.000
							DEL	HC	−16.77[a]	1.79	<.001
YoEdu	11.4 ± 2.5	11.7 ± 3.4	12.3 ± 1.6	13.0 ± 4.0	18.140	<.001	DELSCZ	SCZ	−.34	.82	1.000
								DEL	−.95	.98	1.000
								HC	−1.64	.82	.277
							SCZ	DEL	−.61	.57	1.000
								HC	−1.30[a]	.18	<.001
							DEL	HC	−.69	.57	1.000
PANSS PS	18.8 ± 5.6	16.0 ± 6.6	9.6 ± 2.7	7.2 ± .6	473.575	<.001	DELSCZ	SCZ	2.80	1.09	.063
								DEL	9.12[a]	1.31	<.001
								HC	11.56[a]	1.09	<.001
							SCZ	DEL	6.32[a]	.75	<.001
								HC	8.76[a]	.24	<.001
							DEL	HC	2.44[a]	.76	.008
PANSS NS	20.8 ± 5.2	21.8 ± 8.4	12.1 ± 3.6	7.4 ± 1.4	764.665	<.001	DELSCZ	SCZ	−1.01	1.39	1.000
								DEL	8.66[a]	1.67	<.001
								HC	13.39[a]	1.40	<.001
							SCZ	DEL	9.67[a]	.96	<.001
								HC	14.40[a]	.30	<.001
							DEL	HC	4.73[a]	.97	<.001

(Continues)

TABLE 1 (Continued)

(a)							*Post hoc*				
Continuous variables	**DELSCZ *N* = 20**	**SCZ *N* = 893**	**DEL *N* = 43**	**HC *N* = 780**	***F***	***p***	**Group comparison**		**Mean difference**	**Standard error**	***p***
PANSS GP	43.3 ± 8.4	37.1 ± 11.6	29.3 ± 6.5	17.5 ± 2.8	738.952	<.001	DELSCZ	SCZ	6.12	1.95	.010
								DEL	13.97[a]	2.33	<.001
								HC	25.74[a]	1.95	<.001
							SCZ	DEL	7.85	1.34	<.001
								HC	19.63[a]	.42	<.001
							DEL	HC	11.77[a]	1.35	<.001
PANSS Tot	82.8 ± 16.3	74.8 ± 22.6	51.0 ± 10.9	32.1 ± 3.8	944.010	<.001	DELSCZ	SCZ	7.90	3.75	.211
								DEL	31.75[a]	4.49	<.001
								HC	50.70[a]	3.75	<.001
							SCZ	DEL	23.85[a]	2.59	<.001
								HC	42.79	.81	<.001
							DEL	HC	18.95[a]	2.60	<.001
MCCB Comp[b]	−1.4 ± .7	−1.2 ± .9	−1.0 ± .8	.1 ± .7	379.854	<.001	DELSCZ	SCZ	−.21	.18	1.000
								DEL	−.47	.21	.177
								HC	−1.53[a]	.18	<.001
							SCZ	DEL	−.26	.12	.227
								HC	−1.31[a]	.04	<.001
							DEL	HC	−1.06[a]	.13	<.001

				t	
IQ	83.5 ± 17.5		87.5 ± 14.1	.981	.331
Onset	19.9 ± 5.1	24.1 ± 7.2		2.578	.01
DoI	6.5 ± 4.9	15.9 ± 10.4		3.995	<.001

TABLE 1 (Continued)

Categorical variables	DEL SCZ $N=20$	SCZ $N=893$	DEL $N=43$	HC $N=780$	χ^2	p
Sex						
Female	20.0% ($N=4$)	30.6% ($N=273$)	32.6% ($N=14$)	51.5% ($N=402$)	80.724	<.001
Male	80.0% ($N=16$)	69.4% ($N=620$)	67.4% ($N=29$)	48.5% ($N=378$)		
Treatment						
No AP	.0% ($N=0$)	3.1% ($N=28$)			2.570	.463
SGA	85.0% ($N=17$)	69.5% ($N=621$)				
FGA	10.0% ($N=2$)	13.8% ($N=123$)				
FGA + SGA	5.0% ($N=1$)	13.5% ($N=121$)				

Note: Mean ± standard deviations are reported.

Abbreviations: AP, Antipsychotic drugs; DoI, Duration of Illness; FGA, First Generation Antipsychotic drug; GP, General Psychopathology; IQ, Intelligent Quotient; MCCB Comp, MCCB Composite score; NS, Negative Symptoms; Onset, age at the first episode of psychosis; PANSS, Positive And Negative Syndrome Scale; PS, Positive Symptoms; SGA, Second Generation Antipsychotic drug; Tot, Total PANSS scores; YoEdu, years of education.

[a]Significant post-hoc comparison.

[b]$\tilde{\chi}$-score.

differences were observed between SCZ and DEL SCZ for exposure to different antipsychotic treatments (Table 1b).

Sex composition significantly differed between the groups (Table 1b), due to HC group having more female participants with respect to DEL SCZ and SCZ ($p < .05$).

Difference among groups in social cognition and functioning

To test for Social Cognition between-group differences a MANCOVA was implemented, considering Age and MCCB Composite as covariates, and each TASIT score as dependent variables. This analysis resulted to be statistically significant (Pillai Trace = .811; Wilks' Lambda = .189; Hotelling Trace = 4.299; Roy's largest Root = 4.299; $F_{(3,1711)} = 2451.769$, $p < .001$). Group as a variable showed significant results on Multivariate Tests ($p < .001$; Table S1a). However, both Age ($p = .002$) and MCCB Composite ($p < .001$) reached statistical significance. When considering Effects between Subjects Tests, the corrected model showed significance for each dependent variable: *Emotion Recognition*, $F = 261.549$, $p < .001$; *Minimal Social Inference*, $F = 313.237$, $p < .001$; *Social Inference Enriched*, $F = 270.113$, $p < .001$; and TASIT Total, $F = 381.468$, $p < .001$.

Age showed a significant effect on *Emotion Recognition* ($F = 11.145$, $p < .001$). MCCB Composite score was found to have a significant effect on each TASIT partial score, as well as on the Total score ($p < .001$; Table S1b). Also the Group variable, as expected, showed a significant impact on each dependent variable ($p < .001$; Table S1b).

Post-hoc comparisons showed the following significant differences in mean TASIT scores (corrected for MMCB Composite and Age) between groups. The three clinical groups performed worse than HC on *Emotion Recognition* (DEL SCZ and SCZ vs. HC, $p < .001$; DEL vs. HC, $p = .014$), *Minimal Social Inference* ($p < .001$) and TASIT Total Score (DEL SCZ and SCZ vs. HC, $p < .001$; DEL vs. HC, $p = .004$; Figure 1). SCZ scored lower on the *Social Inference Enriched* subscale compared to DEL ($p = .004$) and HC ($p < .001$).

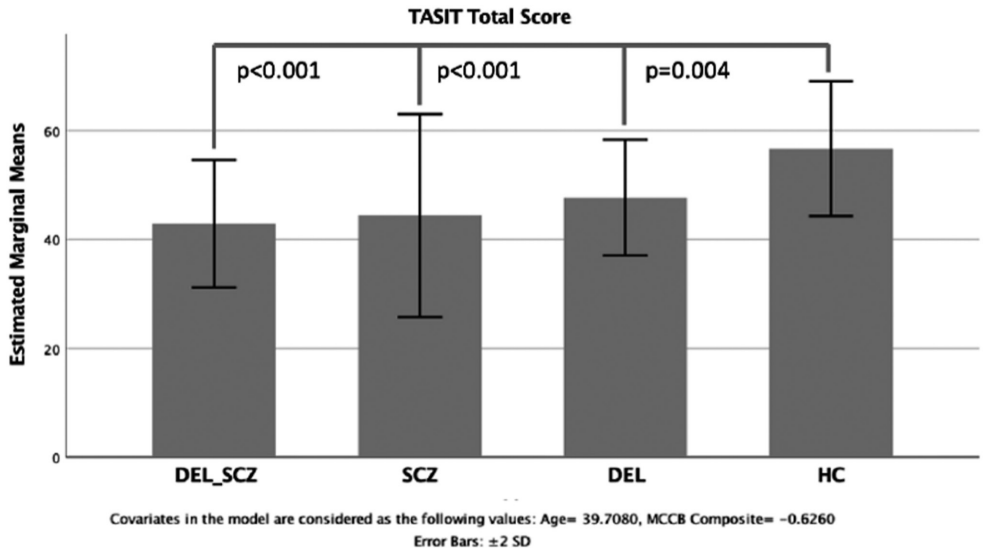

FIGURE 1 Estimated Marginal Means of TASIT Total Score corrected for MCCB and Age covariates in each group. *Post-hoc* statistical significances are illustrated. DEL = patients with 22q11.2 Deletion Syndrome without schizophrenia; DEL_SCZ = patients with 22q11.2 Deletion Syndrome and schizophrenia; HC = healthy controls; MCCB_Comp = MATRICS Consensus Cognitive Battery Composite score; SCZ = patients with schizophrenia; TASIT Tot = The Awareness of Social Inference Test Total score.

To investigate between-group differences in Functioning a MANOVA was run, with SLoF scores as dependent variables. The analysis was significant ($p < .001$) and Group variable showed a significant effect at Multivariate Tests ($p < .001$; Table S2).

Effect between Subjects test showed a significant impact ($p < .001$) of Group factor for each dependent variable (*Self-Maintenance, Social Functioning, Community Living Skills*, and SloF Total score).

Post-hoc comparisons showed for the DEL_SCZ group significantly lower scores on *Self Maintenance* compared to each of the other groups (SCZ, $p < .001$; DEL, $p = .023$; HC, $p < .001$). Furthermore, the SCZ and DEL groups showed significant deficit in *Self Maintenance* compared to HC ($p < .001$).

Regarding the *Social Functioning* area (Figure 2), the DEL_SCZ and SCZ groups scored significantly lower compared to DEL ($p < .007$ and $p = .015$, respectively) and HC ($p < .001$). Considering *Activities* and *Community Life*, DEL_SCZ scored significantly lower with respect to any other group (SCZ, $p = .004$; DEL, $p = .004$; HC, $p < .001$), while both DEL and SCZ groups scored significantly worse than HC ($p < .001$).

Considering global real-life functioning (SLoF Total Score; Figure 3), DEL SCZ scored significantly lower compared to the other groups (SCZ, $p = .004$; DEL, $p = .003$; HC, $p < .001$). The SCZ group was found to have a similar level of global functioning compared to the DEL group, and both scored significantly lower on SLoF Total scores than HC ($p < .001$).

Functioning and social cognition

A regression analysis was conducted to understand the impact on functioning of social cognition deficit, but also of clinical parameters such as DoI, severity of symptoms and other cognitive dysfunctions. Using the Stepwise method, in DEL_SCZ two models provided significant results (Table S3). In the first one ($F = 19.103$, $p < .001$), the predictor was the PANSS Total score ($R = .718$, $R^2 = .515$, F change $= 19.103$, $p < .001$; Figure 4). However, the model remained significant ($F = 14.240$, $p < .001$) when TASIT Total

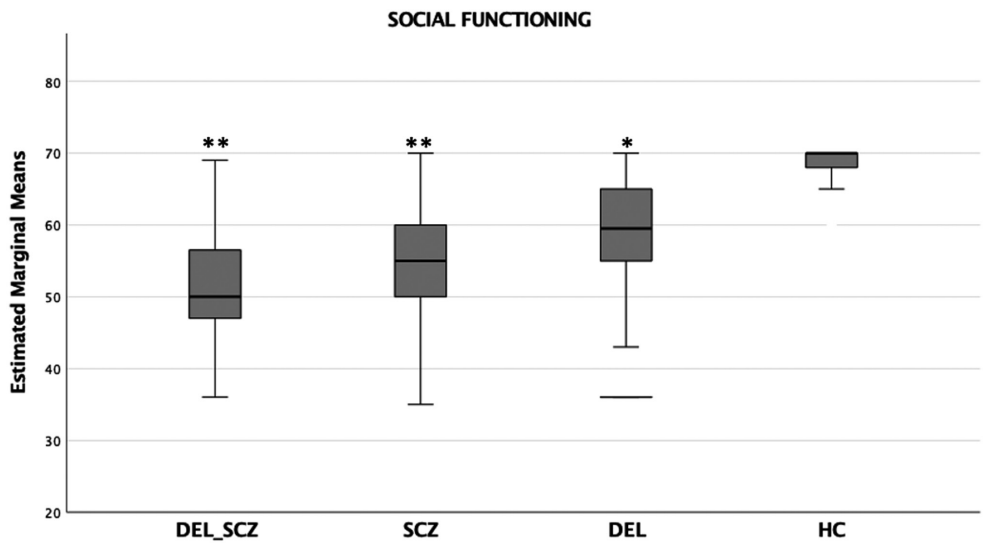

FIGURE 2 Estimated marginal means of SLoF Social Functioning scores for each group. * DEL group showed significantly lower scores with respect to HC ($p < .001$). ** DEL_SCZ and SCZ groups scored significantly lower on SLoF Social Functioning compared to DEL ($p < .007$ and $p = .015$, respectively) and HC ($p < .001$). Errors bars = ±2 Standard Errors. DEL = patients with 22q11.2 Deletion Syndrome without schizophrenia; DEL_SCZ = patients with 22q11.2 Deletion Syndrome and schizophrenia; *F*_Social = Social Functioning scores on the Specific Levels of Functioning (SLoF); HC = healthy controls; SCZ = patients with schizophrenia.

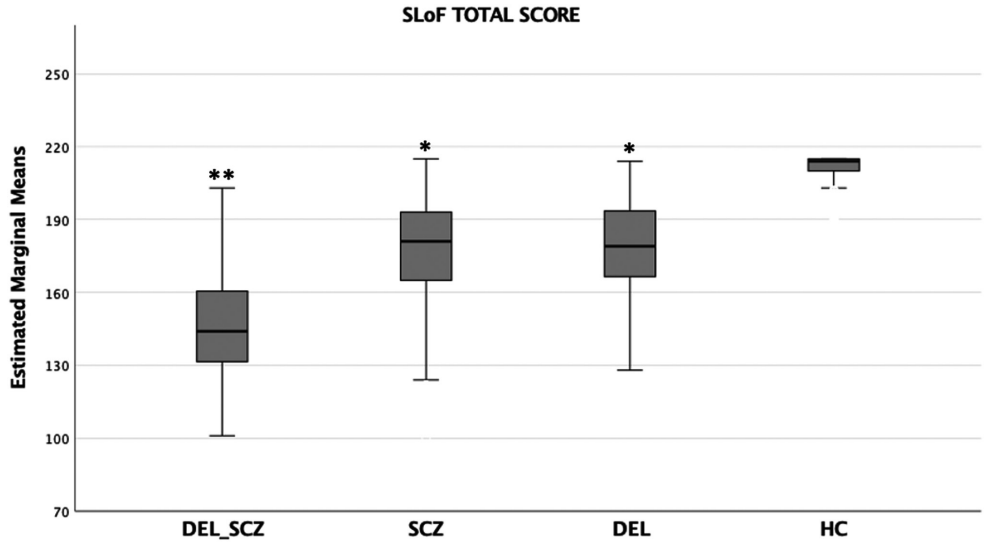

FIGURE 3 Estimated marginal means of SLoF Total scores for each group. * SCZ and DEL group showed significantly lower SloF Total scores with respect to the HC group ($p < .001$). ** DEL_SCZ group showed significantly lower SloF Total scores compared to all other groups (SCZ, $p = .004$; DEL, $p = .003$; HC, $p < .001$). DEL = patients with 22q11.2 Deletion Syndrome without schizophrenia; DEL_SCZ = patients with 22q11.2 Deletion Syndrome and schizophrenia; *F*_Tot = Total scores on the Specific Levels of Functioning (SLoF); HC = healthy controls; SCZ = patients with schizophrenia.

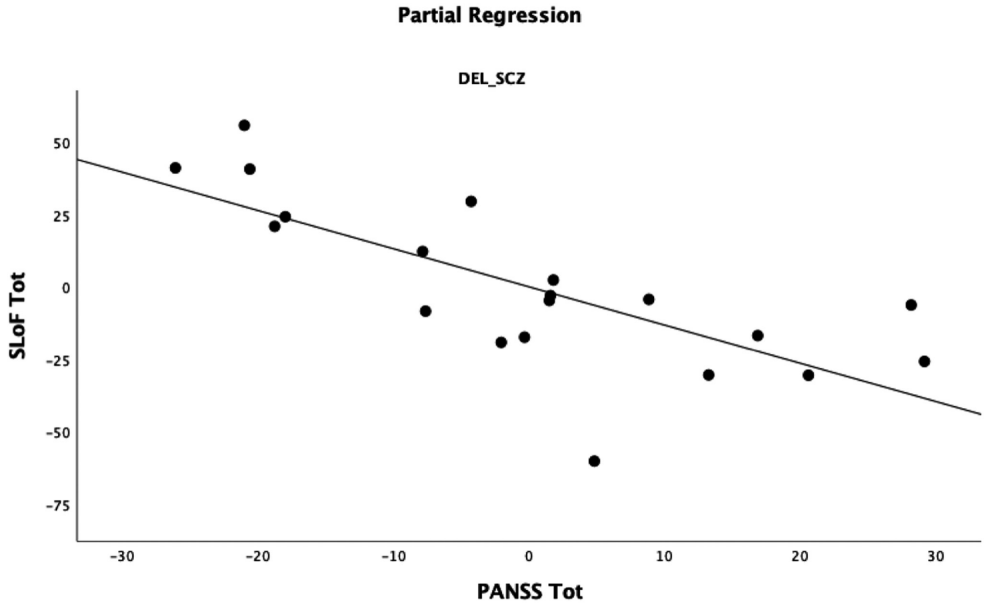

FIGURE 4 Partial Regression showing a significant inverse correlation between SLoF and PANSS Total scores in the DEL_SCZ group. DEL_SCZ = patients with 22q11.2 Deletion Syndrome and schizophrenia; PANSS Tot = Positive And Negative Syndrome Scale Total scores; SLoF = Specific Levels of Functioning.

score was added as a further predictor ($R = .791$; $R^2 = .626$; *F* Change = 5.064; $p = .038$; Figure 5). MCCB Composite score, Age and DoI did not show any significant impact on SLoF Total scores in DEL_SCZ.

In the SCZ group, the model remained significant when all predictors were added (Table S4). PANSS Total score was the first predictor introduced ($F = 286.529$, $p < .001$; $R = .493$; $R^2 = .243$; *F*

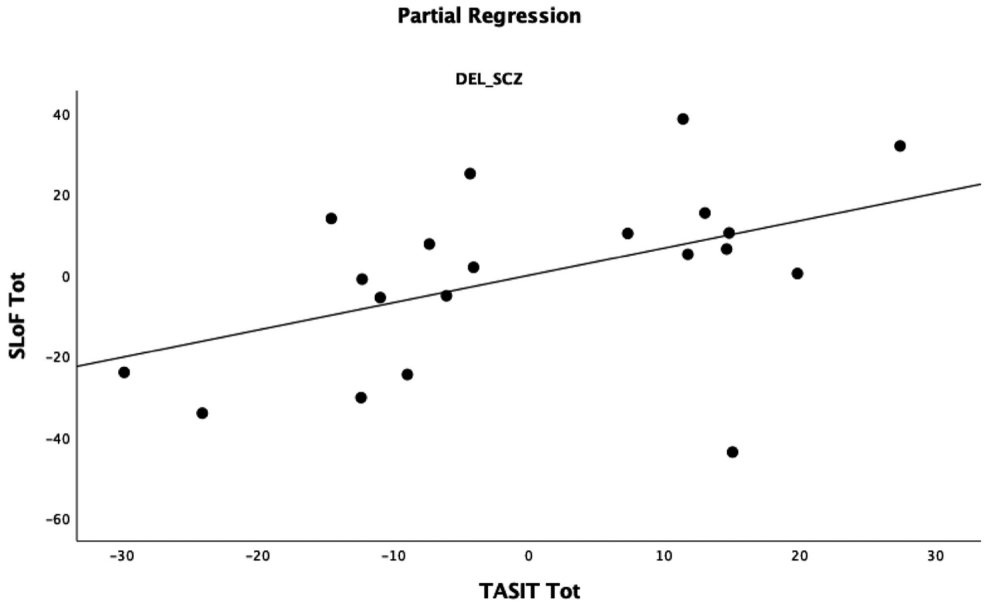

FIGURE 5 Partial Regression showing a significant direct correlation between SLoF and TASIT Total scores in the DEL_SCZ group. DEL_SCZ = patients with 22q11.2 Deletion Syndrome and schizophrenia; SLoF = Specific Levels of Functioning; TASIT Tot = The Awareness of Social Inference Test Total score.

Change = 286.529; $p < .001$). The second model ($F = 198.881$, $p < .001$) was obtained adding MCCB Composite score ($R = .556$; $R^2 = .309$; F Change = 84.410; $p < .001$). The third model ($F = 147.438$, $p < .001$) considered TASIT Total score as third predictor ($R = .576$; $R^2 = .332$; F Change = 31.101; $p < .001$), and DoI also showed a significant impact on SLoF Total score when added to the other variables ($F = 113.803$, $p < .001$; $R = .582$; $R^2 = .339$; F Change = 8.945; $p = .003$). Finally, the model was significant ($F = 93.876$, $p < .001$) also entering Age as a covariate ($R = .588$; $R^2 = .339$; F Change = 8.945; $p = .002$).

In DEL group, only one model was significant ($F = 11.704$, $p < .001$; $R = .472$, $R^2 = .222$, F Change = 11.704, $p = .001$), where MCCB Composite alone was the predictor variable (Standardised Beta Coefficient = .471; $t = .3421$; $p = .001$; C.I. 95% from 4.820 to 18.711).

DISCUSSION

To our knowledge, this study is the first to analyse real-life functioning in a sample of 22q11DS subjects with and without a psychotic disorder compared to a large population of patients with idiopathic schizophrenia and healthy controls. Our findings showed similar deficits in global functioning between non-psychotic 22q11DS and patients with idiopathic schizophrenia, compared to HCs; 22q11DS patients with psychosis revealed an even more serious decline in functioning with respect to the other clinical groups. Furthermore, we observed that both symptom severity and the extent of SC deficits were involved in the level of functioning of DEL SCZ patients. In line with our hypothesis, these two variables were found to contribute to functioning outcome modulation in patients with idiopathic schizophrenia. On the other hand, the neurocognitive performance was the only predictor of global functioning outcome in 22q11DS patients without psychosis.

Our 22q11DS sample consisted of 63 patients, among which, 20 received a diagnosis of a schizophrenia spectrum disorder. A large population of idiopathic schizophrenia patients ($N = 893$) and HCs ($N = 780$) were enrolled. As expected, 22q11DS patients were significantly younger compared to the

other groups, since the majority of individuals with 22q11DS were referred to the Psychiatric Outpatient Service from the Paediatric Unit after turning 16; instead, the SCZ group mostly consisted of patients affected by a chronic illness. Differences in DoI further confirmed this; the larger part of DEL SCZ patients was evaluated at the time of their first psychotic episode, or just right after. No differences were observed between 22q11DS patients and HCs in educational level, likely due to the school support that Italian students with disabilities receive since early age in order to achieve educational qualification.

Schizophrenia is a severe mental disorder which greatly impacts Public Health. It constitutes the 12th cause of disability within the Global Burden of Disease Project (Charlson et al., 2018). Deficits in several major areas of everyday life are well-known (Galderisi et al., 2014) and social functioning deficits have been clearly established as a core feature of the clinical presentation of schizophrenia and of its premorbid phase (Burns & Patrick, 2007). Butcher et al. (2012) found that having schizophrenia for 22q11DS individuals has a significant impact on functional abilities, more than suffering from other psychiatric conditions and even more than having a congenital heart disease. Other reports on adult 22q11DS individuals consistently found functional deficits largely impacting independent life (Butcher et al., 2012).

Interestingly, we showed a similar global functioning deficit between 22q11DS without psychosis and idiopathic schizophrenia, as seen in Figure 3. Remarkably, we found in 22q11DS without psychosis a significant deficit in social functioning with respect to HCs and an even more severe impairment in psychotic groups independently from 22q11DS condition. These findings confirmed the endophenotypic character of disability in social functioning in schizophrenia, which appear closely linked to the biological/genetic component of the disorder (Lattanzi et al., 2018).

Interesting results were obtained from differences in symptom severity evaluated through the PANSS. Apart from the expected finding that the groups with psychosis had more Positive and Negative symptoms, two results were noteworthy. First, 22q11DS patients without a diagnosis of a psychotic disorder showed significantly more Positive and Negative symptoms compared to HCs. This is in line with the fact that people with 22q11.2DS are at high genetic risk for psychosis, increasing the chance to observe an attenuated psychotic syndrome at the time of assessment; moreover, it is important to consider that the mean age of this group coincides with the usual age of onset of premorbid symptoms of schizophrenia. Previous studies found subthreshold psychotic symptoms (Tang et al., 2014) or schizotypal traits (Fonseca-Pedrero et al., 2016) in 22q11DS samples. Indeed, some authors proposed to consider ultra-high risk symptoms as "trait-like phenomena" in patients with 22q11DS (Armando et al., 2017). The second remarkable result is that the DEL SCZ group seems to have more serious general psychopathology symptoms compared to SCZ. DEL SCZ patients would be at their first episode of psychosis and are likely to be experiencing high levels of emotional distress associated with the psychotic onset (i.e., anxiety). Prodromal periods are predominated by abnormal self-experiences which cannot be considered frankly psychotic, but impinge on general psychopathology. This would impact general psychopathology scores. On the other hand, the majority of chronic patients may be experiencing flattened affect and emotional blunting, which do not encode for general psychopathology, but add to the negative symptom dimension. Another explanation could rely on the possibility that 22q11DS patients with psychosis had more comorbidity, for example, anxiety disorders (Schneider et al., 2014; Sim et al., 2006). Furthermore, 22q11DS patients were found to have an earlier psychotic onset in our sample compared to SCZ patients. Previous studies had found a typical (Bassett et al., 2003) or later age at onset in schizophrenia (Murphy et al., 1999), but more recent studies confirm our finding of an early psychotic episode (Vorstman et al., 2006); this would be consistent with the high amount of 22q11.2 microdeletions found in patients with childhood-onset schizophrenia (Sporn et al., 2004).

Regarding neurocognitive performance, no significant differences were found among the three clinical groups which in turn proved to be impaired compared to HCs. Neurocognition deficit in 22q11DS patients is extensively reported in the literature (Moberg et al., 2018). In our study, we found in 22q11DS patients a deficit similar to that of a large population of patients with idiopathic schizophrenia, as compared to typically developing individuals. Moreover, we observed no differences between 22q11DS patients with and without psychosis. Groups differed in sex composition, with SCZ groups containing

more males. However, a previous analysis on the same sample (Accinni et al., 2021) did not find any effect of sex on SC, thus such difference was not further taken into account here.

SC performance, as assessed through TASIT, proved to depend on other neurocognitive abilities, and an impact of Age was shown only for the *Emotion Recognition* domain. Despite the role of general cognitive functioning in determining TASIT performance, differences among groups in SC were confirmed when correcting for this variable. *Post-hoc* tests showed a well-defined significant deficit in *Emotion Recognition* and *Minimal Social Inference* for all the three clinical groups with respect to controls, with no differences among patient samples. Similar results were obtained for the global TASIT performance. However, when examining the *Social Inference Enriched* subscale, a significant difference emerged between the SCZ group and both DEL and HC groups. No significant difference was found between the 22q11DS groups and HCs. We may partially explain such findings considering that this section of TASIT requires more neurocognitive abilities to interpret and reply. The difference in SC would be smoothed out by adjusting for MCCB scores. These results are in line with previous studies which have described SC deficits, especially in regard of Emotion Perception and Theory of Mind dimensions, as a core endophenotype of schizophrenia (Rocca et al., 2016; Snitz et al., 2006). Additionally, the present study confirmed that though some neurocognitive processes are involved in the execution of SC tasks, neurocognition and social cognition can be considered as distinct constructs (Mehta et al., 2013). Our results confirmed findings from a recent study of a specific SC deficit in 22q11DS independently from cognitive impairment and psychiatric comorbidity (Jalal et al., 2021) and most of the reported studies confirmed deficits in several domains of SC in 22q11DS individuals (Frascarelli et al., 2020; Milic et al., 2021). The current study highlighted a global SC deficit in individuals with 22q11.2DS without psychotic symptoms, which is of the same magnitude as both SCZ groups. It could be argued that the same neurodevelopmental defects, linked to the genetic risk for schizophrenia, determine neurobiological alterations with functional dysfunctions, which are in turn related to poor social skills. According to our hypothesis, these impairments seem to determine a worsening of daily functioning.

The SloF data showed that the *Self-Maintenance* and *Community Living Skills* domains, which compose Global Functioning, are similarly impaired in the DEL and SCZ groups, compared to HCs. On the other hand, individuals with SD22q11 deletion and psychosis shown an even more pronounced impairment in the same domains, not only compared to HCs, but also with respect to the other clinical groups, i.e., DEL and SCZ. Data showed that having both 22q11 deletion and a psychotic disorder diagnosis amplifies functional impairment, except in the *Social Functioning* domain, where both groups with psychosis, with or without 22q11 deletion, scored significantly lower than DEL and HCs.

We aimed to clarify whether Social Cognition would contribute to the deficits in functioning observed in SCZ groups; our hypothesis was that this relation would be present well before psychotic onset in 22q11DS as a premorbid feature of a subsequent possible psychotic transition. Several predictors were entered into the regression analysis, as suggested by the literature (Galderisi et al., 2014). For the DEL_SCZ group, the variables that significantly predicted the outcome in terms of SLoF Total scores were severity of symptoms, as assessed through the PANSS, and secondly, the degree of SC impairment. These two variables appeared to reliably predict also idiopathic schizophrenia, along with neurocognitive performance, DoI, and age.

Limitations

Despite several advantages that include having an adult sample with a rare genetic condition, employing large groups of schizophrenia patients and using a valid instrument such as the SLoF (Mucci et al., 2014), the present study has several limitations, namely the small sample size of 22q11DS groups, due to the relative rarity of the deletion. However, this has been addressed through adequate statistics, by applying appropriate corrections. Missing data regarding Attention/Vigilance domain performance may have impacted our results. However, we showed that TASIT performance is related to many other executive functions, and sustained attention could impact only the *Social Inference Enriched* part. Furthermore,

we did not consider the possible effects of psychopharmacological interventions. Moreover, the DEL group can be considered as a heterogenous group, as it is composed of patients suffering from psychiatric conditions other than the psychoses, of individuals with no psychiatric symptoms at all, but also of some individuals with subthreshold psychotic symptoms or at clinical high risk for psychosis, which has not been evaluated with specific instruments. One future objective will be recruiting more 22q11DS individuals so as to be able to separate another group of 22q11DS patients with Attenuated Psychotic Symptoms. Another limitation of the present work was the absence of comorbidity data in view of the fact that previous studies showed differences between groups: i.e., autism trait and ADHD were recurrent in 22q11DS and diagnosis of depression was more frequent in idiopathic schizophrenia (Schneider et al., 2014; Sim et al., 2006). Finally, the present work consisted of a cross-sectional observational study; a longitudinal design would better allow to describe more accurately the predictive value of SC deficits on global functioning.

SUMMARY AND CONCLUSIONS

Our first hypothesis was confirmed, as SC performance impacted real-life functioning not only in idiopathic schizophrenia patients, but also in those with 22q11DS and psychosis. Our results suggested that SC deficits in the genetic-risk sample constitute an endophenotype, given their presence to a similar extent both in the DEL and SCZ groups (Figure 1); however, these deficits do not relate strictly to the functioning impairments observed in these patients. Indeed, neurocognitive performance deficit emerged from the regression analysis as the only significant predictor of impaired functioning for patients with 22q11DS without psychosis. SC deficit could be considered as an endophenotype for schizophrenia, but it contributes to decreased everyday functioning in these patients only after the onset of psychosis. We may suppose that DEL individuals who will not develop a psychotic disorder will be likely able to effectively cope with their deficits, thus preserving an acceptable real-life functioning (Armando et al., 2018).

Our results point to the possible utility of evaluating for these populations specific rehabilitation programmes, such as Social Skills Training and Cognitive Remediation. The aim for providing such programmes to people who are at a premorbid stage of psychosis or having a high genetic risk condition would be to prevent the onset of psychosis or, at least, to diminish the impact of the illness on functioning by means of personal resource empowerment.

AUTHOR CONTRIBUTIONS

Marianna Frascarelli: Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Antonino Buzzanca:** Formal analysis; writing – review and editing. **Luca Carlone:** Writing – original draft; writing – review and editing. **Francesco Ghezzi:** Writing – original draft; writing – review and editing. **Antonella Moschillo:** Writing – original draft; writing – review and editing. **Georgios D. Kotzalidis:** Methodology; visualization; writing – review and editing. **Paola Bucci:** Methodology; writing – review and editing. **Giulia Maria Giordano:** Methodology; writing – review and editing. **Martina Fanella:** Resources; writing – review and editing. **Carlo Di Bonaventura:** Resources; writing – review and editing. **Carolina Putotto:** Resources; writing – review and editing. **Bruno Marino:** Supervision; writing – review and editing. **Massimo Pasquini:** Supervision; writing – review and editing. **Massimo Biondi:** Supervision; writing – review and editing. **Fabio Di Fabio:** Conceptualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT
All authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL
All participants 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 Sapienza University, Rome, Italy. All data were anonymised.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Tables S1–S4

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