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Social cognition deficit and genetic vulnerability to schizophrenia in 22q11 deletion syndrome

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Abstract

Introduction. 22q11.2 microdeletion syndrome (22q11DS) is associated with a 25% risk of psychotic onset.

Materials and methods. The sample consist of 120 subjects: 39 schizophrenics (SCZ); 20 siblings of schizophrenic patients (SIB); 34 22q11DS non-psychotic patients (DEL); 17 22q11DS psychotic patients (DEL_scz); 30 control subjects (CS). Social cognition was evaluated with the awareness of social interference test. Intelligence Quotient (IQ) was calculated with Wechsler Adult Intelligence Scale. TASIT (Awareness of Social Inference Test) performance was analyzed via MANOVA, including IQ as covariate.

Results. Group and IQ showed significant effect ($p < 0.001$; $p = 0.037$). The only TASIT variables where IQ showed no effect were paradoxical sarcasm; sincerity; lie. In sincerity, CS group shows a better performance than both 22q11DS groups ($p < 0.05$). In paradoxical sarcasm and lie, CS group performed better than each clinical group ($p < 0.05$). Regarding lie, DEL group was worst also respect to SCZ group ($p = 0.029$).

Conclusions. Our results show a specific social cognition deficit in 22q11DS and schizophrenia.

Key words

- schizophrenia
- 22q11 deletion syndrome
- social cognition
- psychosis

INTRODUCTION

22q11.2 deletion syndrome, also known as velocardiofacial syndrome or DiGeorge syndrome, is the most common microdeletion in humans. This autosomal dominant deletion determines a syndrome which is expressed in 1:4000 live birth [1]. It has a 100% of penetrance but the phenotipic expression is highly variable. Indeed, with 180 characteristics associated, the syndrome is one of the most protean. Some of the most common manifestations of the 22q11DS are: facial dysmorphias, cardiovascular congenital abnormalities, palatal defects, thymus hypoplasia with primary immunodeficiency, ipoparathyroidism [2]. Organs and tissues affected have all origin during embryo development from neural crest cells [3]. The microdeletion of the band 11.2 in the chromosome 22, according to literature, gives a 25% risk of developing a psychotic disorder [4]. More recently, the prevalence of schizophrenia spectrum disorders in 22q11DS has been attested from 23% to 43%, depending on the study. In this deletion syndrome neurobiological factors seem to play a key role in determining psychosis onset, while other triggers, which have a prominent role in idiopathic schizophrenia, have in this case a minor part. Recognizing those factors in a simplified model of schizophrenia, respect to the complex multifactorial model of the disorder in the general population appears as a needful opportunity. During the last decade 22q11.2 deletion syndrome (22q11DS) has been studied as the best genetic and biological model of vulnerability to schizophrenia, which provides a unique method to unveil the etiopathogenesis of psychosis and to arrange new strategies of prevention. The first clinical documentation of the syndrome dates back to 1978 [2], but it is only from 1992, when the first report on psychiatric manifestations associated was published, that the attention of research is focused on cognitive and behavioural phenotypic aspects [5]. Studies on animal models showed that many of the deleted genes in 22q11DS are physiologically expressed during the cerebral development and are responsible for a correct neurogenesis. The abnormal brain maturation consequent to the aplodeficiency of those genes may be the biological cause of

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the behavioural, neurocognitive and psychopathological phenotype expressed [6, 7]. The neurocognitive profile has been well-defined and it appears highly variable both inter-individuals than during the life of a single subject. During infancy, motor delay and language difficulties are commonly observed [8]. In the school age learning disabilities are frequent. The cognitive functions more often compromised are mathematical reasoning [9] and visuo-spatial abilities [10]; attention, executive functions and working memory deficits have been frequently reported [11]. Most of the patients has a borderline cognitive delay (IQ from 70 to 84), while only one third has a moderate mental retardation [12]. Temperamental and behavioral typical aspects are social difficulties, impulsiveness or shyness [8]. Also the psychiatric phenotype of the syndrome has been now clearly described [13]; individuals have significantly higher incidence rate compared to general population for several mental disorders [14]. Previous studies indicated that up to one third of adolescent/young adults develops a schizophrenic or schizoaffective disorder [14].

Schizophrenia is considered the most severe of all psychiatric pathologies, occurring in 1% of the general population. It has a multifactorial pathogenesis. The genetic component is of evident importance: the risk of illness with a schizophrenic sibling is 8.5%, 13.8% with a parent and 36.6% when both parents are affected. The concordance rate in twins is 57.7% for the homozygous and 5.6% to 12% for the dizygotic. In second grade relatives of schizophrenics, the percentages are referred to range from 2% to 2.8% [15]. It is relevant that in 22q11DS psychotic symptoms and correlated manifestations, included neurocognitive profile, are not different from schizophrenia characteristics in general population: studies didn't find any difference in onset age, positive or negative symptoms and global functioning [16, 4]. It has been estimated that deletion 22q11.2 is responsible for 0.75% of schizophrenia cases in the general population [4]. However, mutations or polymorphisms in genes which map in the 11.2 band of chromosome 22 could contribute more widely to determine vulnerability to schizophrenia in general population.

Patients with 22q11 deletion syndrome (22q11DS) offers a homogeneous population with a genetic risk of schizophrenia whose study could help in identifying schizophrenia endophenotypes with better accuracy and validity. The deleted region could permit to detect the genes that might be involved in the neurodevelopmental and functional alterations that are risk factors for schizophrenia. Amongst the genes of the deleted region, several have been identified, some of which are present in a mutated form also in patients affected with schizophrenia. Reticulon 4 Receptor (RTN4R) encodes for a protein which inhibits axonal sprouting and is involved in neuronal plasticity [17, 18]. DiGeorge Critical Region gene 8 (DGCR8) it's a gene involved in regulating the genetic transcription through miRNA. DGCR8 deficiencies can cause alterations in the morphology of synapses in the prefrontal cortex [19], hippocampus [20], thalamocortical pathway [21, 22] and throughout the connections between the lateral thalamus and the amygdala [23]. Proline dehydrogenase 1 (PRODH) and catechol-O-methyltransferase (COMT) are enzyme-encoding genes involved with the metabolism of neurotransmitters [24]; in both cases the enzymatic deficiency leads to an increase in dopaminergic transmission. PRODH causes an indirect increase of dopamine as compensatory mechanism to glutamate deficiency, normally produced by proline metabolism [25]. COMT on the other hand is directly involved with biogenic amine degradation including dopamine. PRODH and COMT mutations have been correlated to the development of schizophrenia not linked to DiGeorge Syndrome. The reduced expression of these genes is also associated with negative symptoms and social withdrawal in schizophrenia [26].

Social cognition deficits are a well-known cognitive characteristic of schizophrenia and it is well established that social dysfunction is also a common feature of the 22q11DS profile [8]. Social cognition consists of a wide spectrum of functions that control social interactions with other people; it is the result of a set of mental operations organized in domains, Theory of Mind being the main one (ToM), which is the ability to comprehend other people's mental functions through deducing their states of mind [27]. Bora *et al*. found very interesting data through meta-analysis on the studies that inquired into the performance task on ToM in subjects at their first psychotic episode, high clinical risk and high genetic risk [28]. Results show a deficiency comparable to those of chronic patients for the first group, while the performance across the other two groups was intermediate between sanity tests and patients at their first episode. The other components of the social cognition construct are: social perception and social knowledge, as the abilities to understand society rules and roles and the nature of relationships between people and of goals that guide social interactions; attributional bias, or how people deduce the reasons of others' actions; emotional processing, as the way people recognize emotions. It has been observed that social cognition, usually considered as a whole, has an important role in quality of life in schizophrenia patients [29]. The Italian Network for Research on Psychoses [30] found through a network analysis that social cognition deficits are most of the core of schizophrenia, more than positive, negative, and disorganization symptoms. These results highlight the importance of social cognition interventions, such as social skills training, to improve outcome of schizophrenia patients.

The paradigm of social cognition has become ever more studying in 22q11DS [31]. Weinberger *et al.* [32] found more severe deficits in social cognition in psychotic respect to non-psychotic subjects. Jalbrzikowski *et al*. [33] observed a correlation between ToM and positive symptoms. However executive functions and global intellectual functioning could have an important role in social cognition deficit; it has been demonstrated that a basic dysfunction that implies a global intellectual and executive deficit, lead to a weak social cognition [34]. Several findings connected neurocognition and social cognition of 22q11.2 DS schizophrenic patients [31]. Facial emotion recognition deficit, apparently due to altered visual processing in 22q11DS have a key role in impaired social cognition as well [31].

The aim of the present study is to investigate social cognition deficit in an adult sample of 22q11DS patients, for the first time in literature comparing directly to schizophrenic patients and their siblings, in order to evaluate the role of this cognitive deficit in the genetic vulnerability to psychosis. Our aim is also to disentangle neurocognition deficit from social cognition performance, evaluating the sample also in general intelligence.

MATERIALS AND METHODS

Our sample consists of 140 subjects, consecutively enrolled in Policlinico Umberto I, Sapienza University of Rome, divided in 5 groups: schizophrenic patients negative for 22q11DS (SCZ, N = 20); siblings of schizophrenic patients (SIB, N = 20); 22q11DS subjects with no diagnosis of psychosis (DEL, N = 34); 22q11DS patients with diagnosis of psychotic disorder (DEL_scz, N = 17); control subjects (CS, N = 30). Patients were clinically monitored at our outpatients' services specialised in psychotic disorders and psychiatry disorders in 22q11DS. Healthy controls joined the study through word of mouth. All subjects signed an informed consent approved by Policlinico Umberto I Ethical Committee (Rome, Italy). Data from SCZ and SIB groups were also used in an Italian multicentric study conducted by Italian Network for Research on Psychoses. Diagnosis of psychotic disorder was made employing the structured clinical interview for DSM-IV – patient version (SCID-I-P). Genetic diagnosis was ascertained through fluorescent in situ hybridization (FISH). Exclusion criteria for SCZ group were: brain injuries; neurological disorders; substance abuse. Inclusion criteria for DEL group consisted in: age between 18 and 65 years; absence of psychotic symptoms; deletion of band 11.2 in chromosome 22 confirmed by FISH. Exclusion criteria for DEL group were: brain injuries; neurological disorders; substance abuse. Inclusion criteria for CS and SIB groups were age between 18 and 65 years. Exclusion criteria for CS and SIB groups were: diagnosis of psychiatric disorder in axis I or II; brain injuries; neurological disorders, substance abuse; other medical conditions. General intelligence was assessed in all subjects through IQ measurement by the Wechsler Adult Intelligence Scale (WAIS). For all schizophrenic patients, clinical information was obtained on positive and negative symptoms severity with Positive and Negative Symptoms Scale (PANSS) [34]. Social cognition was evaluated through the Awareness of Social Inference Test (TASIT) [35], which is a ToM test where is requested identification of thoughts, feelings, and intentions of characters of video vignettes, and consists of seven scales (positive emotions, negative emotions, sincere, simple sarcasm, paradoxical sarcasm, sarcasm enriched, lie), organized into three sections: emotion recognition; social inference (minimal); social inference (enriched).

Statistical analysis was conducted on IBM software SPSS (version 24). Differences between groups for continuous variables were calculated with ANOVA and post-hoc test were corrected for multiple comparisons. For categorical variables χ^2 test was used. TASIT performance was compared between groups by means of Multivariate ANOVA, entering in the model all test scales and as nuisance covariates gender, age and IQ. Correlation analysis between TASIT performance and PANSS scores was run with Pearson' partial correlation entering QI as nuisance covariate.

RESULTS

Regarding demographical characteristics *(Table 1)*, samples showed significant difference in mean age ($F = 16.183$; $p < 0.001$). SIB group was significantly older respect to each other group (SIB *vs* CS $p < 0.001$; SIB *vs* SCZ $p = 0.021$; SIB *vs* DEL_scz $p < 0.001$; SIB *vs* DEL $p < 0.001$). Moreover, SCZ group was older respect to DEL group ($p < 0.001$). Groups differed also in gender composition ($X^2 = 14.543$, $p = 0.006$), as CS group had a higher proportion of females. Anova analysis for IQ showed significant differences between groups ($F = 16.854$ $p < 0.001$). Post-hoc analyses revealed a higher QI in CS group respect to the others (CS *vs* SIB $p = 0.015$; CS *vs* SCZ $p < 0.001$; CS *vs* DEL_scz $p < 0.001$; CS *vs* DEL $p < 0.001$). SIB had higher mean IQ level respect to DEL_scz group ($p = 0.009$). No differences in mean IQ was observed between clinical groups SCZ, DEL and DEL_scz *(Table 1)*. No differences were observed in PANSS scores or illness duration between DEL_scz and SCZ groups *(Table 1)*.

Analysis of TASIT performance revealed that the

Table 1
Socio-demographical and clinical characteristics of the sample

Variables	CS (n = 30)		SIB (n = 20)		SCZ (n = 39)		DEL_scz (n = 17)		DEL (n = 34)		Statistics	*p*
Sex (%)	M	F	M	F	M	F	M	F	M	F		
	30	70	70	30	56.4	43.6	76.5	23.5	67.6	32.4	$\chi^2 = 14.543$	0.006*
Age (mean ± sd)	28.9 ± 7.5		42.7 ± 12.9		35 ± 9.9		27.5 ± 6.7		24.3 ± 6.9		F =16.183	< 0.001*
IQ (mean ± sd)	113.5 ± 10.8		99.4 ± 8.8		90.4 ± 18		82.5 ± 19.6		89.1 ± 15.1		F =16.854	< 0.001*
PANSS pos					13.4 ± 4.2		14.2 ± 6.1				t = -0.525	0.602
PANSS neg					20.1 ± 7.3		16.8 ± 6				t = 1.637	0.107
PANSS gen					35.2 ± 8.1		32.3 ± 8.9				t = 1.087	0.282
DoI (mean ± sd)					10.6 ± 8		7.1 ± 5				t = 1.33	0.187

CS: control subjects; SIB: siblings of schizophrenic patients; SCZ: schizophrenics; DEL_scz: psychotic patients; DEL: non psychotic patients.
Sd: standard deviation; IQ: intelligent quotient; pos: positive symptoms; neg: negative symptoms; gen: general psychopathology. *statistical significance.

model corrected for nuisance covariates was statistically significant for all TASIT scales (Wilks' Lambda 0.516; F = 12.948; p < 0.001). Group (Wilks' Lambda 0.379; F = 3.825; p < 0.001) and IQ (Wilks' Lambda 0.869; F = 2.07; p = 0.037) variables showed a significant effect. Group effect was significant for all TASIT scales: positive emotions (F = 6.243; p < 0.001; partial Eta^2 = 0.159); negative emotions (F = 8.2017; p < 0.001; partial Eta^2 = 0.199); emotion recognition (F = 10.258; p < 0.001; partial Eta^2 = 0.237); sincere (F = 3.224; p = 0.015; partial Eta^2 = 0.089); simple sarcasm (F = 11.081; p < 0.001; partial Eta^2 = 0.251); paradoxical sarcasm (F = 17.495; p < 0.001; partial Eta^2 = 0.346), social inference (minimal) (F = 17.945; p < 0.001; partial Eta^2 = 0.352); sarcasm enriched (F = 5.779; p < 0.001; partial Eta^2 = 0.149); lie (F = 10.9; p < 0.001; partial Eta^2 = 0.248); social inference (enriched) (F = 15.853; p < 0.001; partial Eta^2 = 0.325). Age showed a significant effect on the following TASIT scales: paradoxical sarcasm (F = 4.166; p = 0.043; partial Eta^2 = 0.031); social inference (minimal) (F = 5.199; p = 0.024; partial Eta^2 = 0.038); sarcasm enriched (F = 6.903; p = 0.010; partial Eta^2 = 0.050). IQ presented a significant effect on the following TASIT scales: positive emotions (F = 6.320; p = 0.013; partial Eta^2 = 0.046); negative emotions (F = 5.825; p = 0.017; partial Eta^2 = 0.042); emotion recognition (F = 9.274; p = 0.003; partial Eta^2 = 0.066); simple sarcasm (F = 4.381; p = 0.038; partial Eta^2 = 0.032); social inference (minimal) (F = 4.586; p = 0.034; partial Eta^2 = 0.034); sarcasm enriched (F = 10.357; p = 0.002); social inference (enriched) (F = 7.641; p = 0.007).

Post-hoc were conducted for TASIT scales were a significant effect of group was found, without the effect of other nuisance covariates.

CS group showed a significantly better performance in sincere scale of TASIT respect to DEL and DEL_scz groups (respectively p = 0.015; p = 0.049) *(Figure 1)*.

In paradoxical sarcasm scale SIB and CS groups had significantly higher score than SCZ, DEL and DEL_scz groups (CS *vs* SCZ p < 0.001; CS *vs* DEL p < 0.001; CS *vs* DEL_scz p < 0.001; SIB *vs* SCZ p < 0.001; SIB *vs* DEL p < 0.001; SIB *vs* DEL_scz p < 0.001) *(Figure 2)*.

For lie scale a significant better performance of SIB and CS group was observed respect to the other groups (CS *vs* SCZ p = 0.025; CS *vs* DEL p < 0.001; CS *vs* DEL_scz p < 0.001; SIB *vs* SCZ p = 0.026; SIB *vs* DEL p < 0.001; SIB *vs* DEL_scz p < 0.001). Moreover, the SCZ group had a significantly higher score respect to DEL group (SCZ *vs* DEL p = 0.029) *(Figure 3)*.

Partial correlations in SCZ group showed a negative correlation between PANSS Positive Symptoms subscale and Sarcasm Enriched TASIS scale (r = -0.337; p = 0.038) and significant negative correlations between PANSS Negative Symptoms subscale and the following TASIT scales: positive emotions (r = -0.363; p = 0.025); negative emotions (r = -0.482; p = 0.002); emotion recognition (r = -0.557; < 0.001); paradoxical sarcasm (r = -0.438; p = 0.006); social inference (minimal) (r = -0.429; p = 0.007); lie (r = -0.451; p = 0.004); social inference (enriched) (r = -0.449; 0.005). A significant negative correlation was found in DEL_scz group between PANSS Negative Symptoms subscale and social inference (enriched) TASIT scale performance (r = -0.525; p = 0.037). Moreover, in this group, PANSS General Psychopathology subscale score showed a significant negative correlation with TASIT lie scale performance (r = -0.561; p = 0.023).

DISCUSSION

The sample consisted of 140 subjects, divided in 5 groups: 30 healthy subjects with no psychiatric diagnosis, genetic predisposition or familiarity for these conditions (CS); 20 first grade relatives of schizophrenic patients (SIB); 39 patients affected with schizophrenia, non-carriers of the 22q11.2 chromosome microdeletion (SCZ); 34 subjects with 22q11.2 deletion syndrome with no psychotic symptoms (DEL); 17 subjects with 22q11.2 deletion syndrome and diagnosed with a psychotic disorder (DEL_scz).

The family members group is the one with the highest average age, being partially composed of schizophrenic patients' parents (4 subjects out of 20). The SCZ group, having in average 11 years duration of illness, resulted significantly older than DEL, consisting of patients who came under our observation during their early-late adolescence in order to assess risk factors and plan the psychotic onset prevention. No significant age gap has been observed between SCZ and DEL_scz groups.

Besides a slight majority of female subjects in the control group, no significant gender differences have been observed within the groups.

A statistically relevant IQ gap between CS and the other three clinical groups has been observed, in line with literature. However the CS group generally shows a significantly higher IQ compared to the SIB group too; this information could be interpreted with the presence of an intermediate cognitive phenotype in family members in comparison to their schizophrenic relatives. The SIB group also shows a higher IQ than DEL_scz patients, which could be due to a particular severity of cognitive retardation in psychotic patients affected with deletion. These results are coherent with literature. There are no relevant IQ gaps amongst the three clinical groups (SCZ, DEL, DEL_scz). IQ has been taken into account in analyzing TASIT performance differences, with the purpose of discerning the global deficiency of neuro-cognitive skills observed in clinical groups from the specific social cognition deficiency that our study aims to demonstrate being associated to psychosis genetic vulnerability. IQ corrected MANOVA results highlight a significant difference in performance for the following TASIT scales: sincerity; paradoxical sarcasm; lie. The control group shows a significantly better performance in recognizing Sincerity compared to 22q11.2 DS affected patients, regardless of psychosis diagnosis. For TASIT sincere clips, where congruence exists between what the actors are literally saying and the paralinguistic and facial cues, in a previous article [29], schizophrenic subjects do not show differences compared to the control group. Our results show that this specific ToM alteration is peculiar to patients affected with DiGeorge Syndrome. Our hypothesis is that this deficiency is solely observed in DEL groups of the study as it is strictly dependent on social perception anomalies

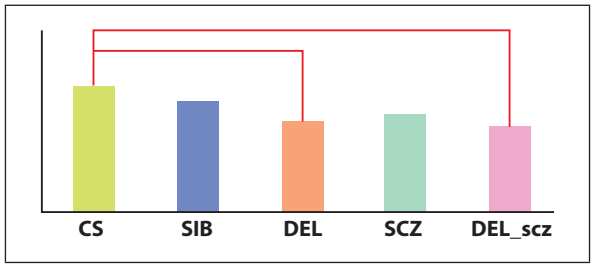

Figure 1
Mean score in TASIT sincere scale for each group. Red lines show significant post-hoc comparisons.
TASIT: Awareness of Social Inference Test; CS: control subjects; SIB: siblings of schizophrenic patients; DEL: non psychotic patients; SCZ: schizophrenics; DEL_scz: psychotic patients.

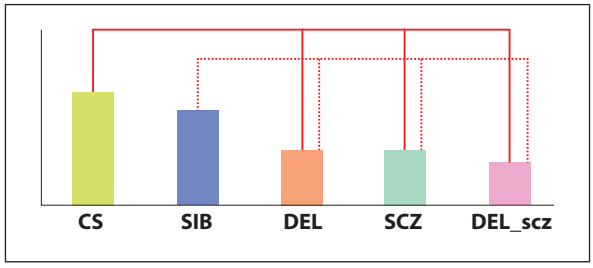

Figure 2
Mean score in TASIT paradoxical sarcasm scale for each group. Red lines show significant post-hoc comparisons.
TASIT: Awareness of Social Inference Test; CS: control subjects; SIB: siblings of schizophrenic patients; DEL: non psychotic patients; SCZ: schizophrenics; DEL_scz: psychotic patients.

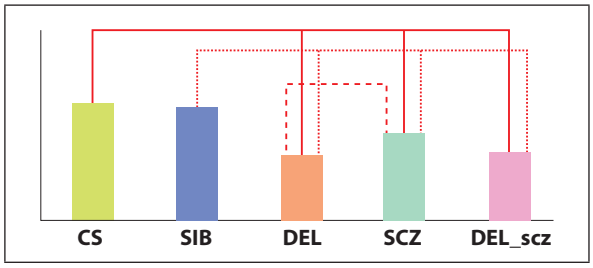

Figure 3
Mean score in TASIT lie scale for each group. Red lines show significant post-hoc comparisons.
TASIT: Awareness of Social Inference Test; CS: control subjects; SIB: siblings of schizophrenic patients; DEL: non psychotic patients; SCZ: schizophrenics; DEL_scz: psychotic patients.

linked to difficulties in processing faces already demonstrated for 22q11.2 deletion syndrome [36].

To evaluate paradoxical sarcasm, some simple scenes are used which only acquire sense if the patient is able to perceive the sarcasm involved in the dialogues (wherein there is no correspondence between what the actors say and what they refer to through their paraverbal language and facial expressions). On this TASIT scale, control and family members groups scored significantly higher than all three clinical groups. Whilst schizophrenic patients' family members perform similarly to healthy subjects, schizophrenic patients groups, both 22q11.2 DS carriers and non-carriers, and 22q11.2 DS patients not affected with psychosis, performed significantly worst in this socio-cognitive function compared to healthy subjects. Hence the recognition of paradoxical sarcasm is particularly compromised in both 22q11.2 DS and schizophrenia, and it might be related to genetic causes of schizophrenia. In comprehending lies, coherently, both control and sibling groups performed significantly better than the other three groups. The SCZ group shows in addition a significantly better performance compared to 22q11.2 DS non-psychotic patients. This result suggests that this specific deficit is representatively prominent in 22q11.2 deletion syndrome, regardless of a diagnosis of schizophrenia.

There are no studies in literature that compare, for socio-cognitive skills, patients affected with schizophrenia or 22q11.2 DS subjects with healthy subjects and first grade family members of schizophrenic patients. Our study is the first in literature to compare all these categories. Resuming our results found specific deficit in interpreting sincere social situations in 22q11DS. Instead, deficit in understanding situation in which people express with paradoxical sarcasm or lying is shared among schizophrenia and 22q11DS. It appears that having both conditions worst this kind of ToM and social perception deficit. We can argue then that this deficit is not depending from a general intelligence gap respect to controls. Other studies found a lack of correlation between IQ and emotion recognition in the 22q11DS, while it was observed in individuals with other developmental disorders such as ASD [37]. However we expected a such deficit, if on a genetic basis, to be present also in SIB group. This could be due to the fact that our SIB group it's composite most of parents, so adult people that had not expressed the psychosis phenotype and evidently not carrying the same risk factors of 22q11DS. In this sense, social cognition deficit appear to be associated with the genetic risk to schizophrenia linked to mutations of genes in the 22q11.2 band. Recently, Antshel *et al*. [38] found that deficits in emotion recognition, in addition to other cognitive functions such as set shifting and reading decoding, were present before the transition to prodromal/overt psychosis in 22q11DS group. Another study found that individuals with 22q11DS showed lower abilities than healthy controls to correctly recognize facial emotions. Authors suggested this difference could be due to abnormal faces recognition in 22q11DS. Studies employing eyetracking infact have consistently shown different patterns of visual exploration during face-processing tasks: compared to typical and idiopathic developmentally delayed control groups, patients with 22q11DS were shown to spend less time on the eyes and more time on the mouth or the nose when examining faces [39]. Moreover they found impairments of specific component of cognitive ToM (*i.e.*, perspective-taking abilities). They interpreted the results as the perspective-taking abilities might have been influenced by higher-order cognitive difficulties, as perspective-taking was shown to engage working memory or cognitive control processes.

The systematic application of tests investigating Social Cognition may contribute to the diagnostic phase

and enable the monitoring of the effect of a rehabilitating intervention.

Performing longitudinal evaluation studies of socio-cognitive skills, in deletion patients, could prove useful to identify possible clinical predictive markers more susceptible to the development of disorders in the schizophrenia spectrum. Because 22q11.2 DS patients are studied since childhood, researches in this field could identify markers that may have a predictive function of the future course of the schizophrenia [33]. In that sense, negative and positive symptoms predictors were studied; the most viable marker for the negative symptoms seems to be impairment of executive functions, while for the positive symptoms it would be the impoverishment in social cognition, particularly ToM alterations, which could build the foundations for the development of interpretative aspects of reality that can trigger delusional symptoms.

Regarding patients affected with schizophrenia but not 22q11 deletion carriers, in literature there are several studies highlighting a correlation between ToM alterations and the insurgence of positive symptoms, whilst no correlation with negative symptoms has been found. The presence of this set of data in literature can serve as a support to the hypothesis of a possible causal correlation between ToM and the subsequent development of psychotic disorder with a prevalent delusional component in the symptomatology.

Our study showed that in SCZ group PANSS positive symptoms subscale shows a negative correlation with sarcasm enriched TASIS scale while PANSS negative symptoms subscale had significant negative correlations with the following TASIT scales: positive emotions; negative emotions; emotion recognition; paradoxical sarcasm; social inference (minimal); lie; social inference (enriched). In DEL_scz group a significant negative correlation between PANSS negative symptoms subscale and social inference (enriched) TASIT scale performance was found. Moreover, in this group, PANSS general psychopathology subscale score shows a significant negative correlation with TASIT lie scale performance. A poorer performance in social cognition is hence associated with more severe negative psychotic symptoms. We may infer that patients with more severe negative severe symptoms tend to be more isolated socially and suffer affective flattening, leading to impaired ability at tuning with other people's emotions and inner state. Nevertheless, given the previously discussed data regarding deficiencies in social cognition in both non-psychotic deletion patients and on a qualitative degree in first grade family members of psychotic patients, it is possible to hypothesize a primary deficiency in social cognition, which leads to the deterioration of social functioning, even before the onset of schizophrenia. Psychotic symptoms will then probably aggravate those deficiencies.

CONCLUSIONS

Our results showed a specific deficit, not influenced by general intelligence impairment, of social cognition in 22q11DS and in schizophrenia, both idiopathic that 22q11DS-linked. Non-psychotic 22q11DS subjects showed similar severity in social cognition deficit to those with schizophrenia. It is possible to argue that genetic alterations in 22q11DS determine a social cognitive deficit, that is more frankly evident after psychosis onset. Social cognition deterioration could be considered an endophenotype of schizophrenia, linked to the genetic etiology of the illness.

Limitation of the present study are the small sample size and the cross-sectional design. Other limits consist in the absence of relevant clinical data, such as treatment and pharmacological interventions. Future study should examine longitudinally neurocognitive functioning of 22q11DS population.

Conflict of interest statements

The authors declare to have no conflicts of interest to disclose.

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REFERENCES

1. McDonald-McGinn DM, Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velo-cardiofacial syndrome). Medicine. 2011;90:1-18.
2. Shprintzen RJ. Velo-cardio-facial syndrome: 30 years of study. Dev Disabil Res Rev. 2008;14:3-10.
3. Scambler PJ. The 22q11 deletion syndromes. Hum mol genet. 2000;9:2421-6.
4. Murphy KC. Schizophrenia and velo-cardio-facial syndrome. Lancet. 2002;359:426-30.
5. Shprintzen RJ, Goldberg R, Golding-Kushner KJ, Marion RW. Late-onset psychosis in the velo-cardio-facial syndrome. Am J Med Genet. 1992;42:141-2.
6. Sivagnanasundaram S, Fletcher D, Hubank M, Illingworth E, Skuse D, Scambler P. Differential gene expression in the hippocampus of the Df1/+ mice: a model for 22q11.2 deletion syndrome and schizophrenia. Brain res. 2007;1139:48-59.
7. Philip N, Bassett A. Cognitive, behavioural and psychiatric phenotype in 22q11.2 deletion syndrome. Behav genet. 2011;41:403-12.
8. Swillen A, Devriendt K, Legius E, Prinzie P, Vogels A, Ghesquiere P, Fryns JP. The behavioural phenotype in velo-cardio-facial syndrome (VCFS): from infancy to adolescence. J Genet Couns. 1999;10:79-88.
9. De Smedt B, Swillen A, Devriendt K, Fryns JP, Verschaffel L, Ghesquiere P. Mathematical disabilities in young primary school children with velo-cardio-facial syndrome. J Genet Couns. 2006;17:259-80.
10. Bearden CE, Woodin MF, Wang PP, Moss E, McDonald-McGinn D, Zackai E, Emannuel B, Cannon TD. The neurocognitive phenotype of the 22q11.2 deletion syndrome: selective deficit in visual-spatial memory. J Clin Exp Neuropsychol 2001;23:447-64.
11. Zinkstok J, van Amelsvoort T. Neuropsychological profile and neuroimaging in patients with 22Q11.2 Deletion Syndrome: a review. Child Neuropsychol. 2005;11:21-37.

12. Chow EW, Watson M, Young DA, Bassett AS. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. Schizophrenia Res. 2006;87:270-8.
13. Baker K, Vorstman JA. Is there a core neuropsychiatric phenotype in 22q11.2 deletion syndrome? Curr Opin Neurol. 2012;25:131-7.
14. Murphy KC. Annotation: velo-cardio-facial syndrome. J Child Psychol Psychiatry. 2005;46:563-71.
15. Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. Br J Psychiatry. 1980;137;497-504.
16. Bassett AS, Chow EW, AbdelMalik P, Gheorghiu M, Husted J, Weksberg R. The schizophrenia phenotype in 22q11 deletion syndrome. Am J of Psychiatry. 2003;160:1580-6.
17. Fournier AE, GrandPre T, Strittmatter SM. Identification of a receptor mediating Nogo-66 inhibition of axonal regeneration. Nature. 2001;409(6818):341-6.
18. Borrie SC, Baeumer BE, Bandtlow CE. The Nogo-66 receptor family in the intact and diseased CNS. Cell Tissue Res. 2012;349(1):105-17.
19. Stark KL, Xu B, Bagchi A, Lai WS, Liu H, Hsu R, Gogos JA. Altered brain microRNA biogenesis contributes to phenotypic deficits in a 22q11-deletion mouse model. Nature Genetics. 2008;40(6):751-60.
20. Ouchi Y, Banno Y, Shimizu Y, Ando S, Hasegawa H, Adachi K, Iwamoto T. Reduced adult hippocampal neurogenesis and working memory deficits in the Dgcr8-deficient mouse model of 22q11.2 deletion-associated schizophrenia can be rescued by IGF2. J Neurosci. 2013;33(22):9408-19.
21. Chun S, Westmoreland JJ, Bayazitov IT, Eddins D, Pani AK, Smeyne RJ, Zakharenk SS. Specific disruption of thalamic inputs to the auditory cortex in schizophrenia models. Science. 2014;344(6188):1178-82.
22. Chun S, Du F, Westmoreland JJ, Han SB, Wang YD, Eddins D, Zakharenko SS. Thalamic miR-338-3p mediates auditory thalamocortical disruption and its late onset in models of 22q11.2 microdeletion. Nature Medicine. 2017;23(1):39-48.
23. Eom TY, Bayazitov IT, Anderson K, Yu J, Zakharenko SS. Schizophrenia-related microdeletion impairs emotional memory through microRNA-dependent disruption of thalamic inputs to the amygdala. Cell Reports. 2017;19(8):1532-44.
24. Wimber M, Schott BH, Wendler FCI, Seidenbecher G, Behnisch T, Macharadze KHT, Bäuml Richardson-Klavehn A. Prefrontal dopamine and the dynamic control of human long-term memory. Transl Psychiatry. 2011;1(7):e15-e15.
25. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet. 1994;344:1398-402.
26. Schneider M, Van der Linden M, Glaser B, Rizzi E, Dahoun S.P. Preliminary structure and predictive value of attenuated negative symptoms in 22q11.2 deletion syndrome. Psychiatry Res. 2012;196(2-3):277-84.
27. Boot E, Booij J, Zinkstok J, Abeling N, de Haan L, Baas F, Linszen D, van Amelsvoort T. Disrupted dopaminergic neurotransmission in 22q11 deletion syndrome. Neuropsychopharmacology. 2008;33(6):1252-8.
28. Bora E, Yucel M, Pantelis C. Theory of mind impairment in schizophrenia: meta-analysis. Schizophrenia Res. 2009;109:1-9.
29. Rocca P, Galderisi S, Rossi A, Bertolino A, Rucci P, Gibertoni D, Montemagni C, Sigaudo M, Mucci A, Bucci P, Acciavatti T, Aguglia E, Amore M, Bellomo A, De Ronchi D, Dell'Osso L, Di Fabio F, Girardi P, Goracci A, Marchesi C, Monteleone P, Niolu C, Pinna F, Roncone R, Sacchetti E, Santonastaso P, Zeppegno P, Maj M; Italian Network for Research on Psychoses. Social cognition in people with schizophrenia: a cluster-analytic approach. Psychol Med. 2016;46:2717-29.
30. Galderisi S, Rucci P, Kirkpatrick B, Mucci A, Gibertoni, D, Rocca P, Rossi A, Bertolino A, Strauss GP, Aguglia E, Bellomo A, Murri MB, Bucci P, Carpiniello B, Comparelli A, Cuomo A, De Berardis D, Dell'Osso L, Di Fabio F, Gelao B, Marchesi C, Monteleone P, Montemagni C, Orsenigo G, Pacitti F, Roncone R, Santonastaso P, Siracusano A, Vignapiano A, Vita A, Zeppegno P, Maj M; Italian Network for Research on Psychoses. Interplay among psychopathologic variables, personal resources, contextrelated factors, and real-life functioning in individuals with schizophrenia: A network analysis. JAMA Psychiatry. 2018;75:396-404.
31. Lattanzi GM, Buzzanca A, Frascarelli M, Di Fabio F. Genetic and clinical features of social cognition in 22q11.2 deletion syndrome. J Neuro Res. 2018;96:1631-40.
32. Weinberger R, Yi J, Calkins M, Guri Y, McDonald-McGinn DM, Emanuel BS, Zackai EH, Ruparel K, Carmel M, Michaelovsky E, Weizman A, Gur RC, Gur RE, Gothelf D. Neurocognitive profile in psychotic *versus* non-psychotic individuals with 22q11.2 deletion syndrome. Eur. Neuropsychopharmacol. 2016;26(10):1610-8.
33. Jalbrzikowski M, Carter C, Senturk D, Chow C, Hopkins JM, Green MF, Galvan A, Cannon TD, Bearden CE. Social cognition in 22q11.2 microdeletion syndrome: relevance to psychosis? Schizophrenia res. 2012;142:99-107.
34. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.
35. McDonald S, Bornhofen C, Shum D, Long E, Saunders C, Neulinger K. Reliability and validity of The Awareness of Social Inference Test (TASIT): a clinical test of social perception. Disabil Rehabil. 2006;28(24):1529-42.
36. Campbell LE, Stevens AF, McCabe K, Cruickshank L, Morris RG, Murphy DGM, Murphy KC. Is theory of mind related to social dysfunction and emotional problems in 22q11.2 deletion syndrome (velo-cardio-facial syndrome)? J Neurodev Disord. 2011;3(2):152-61.
37. McCabe KL, Melville JL, Rich D, Strutt PA, Cooper G, Loughland CM, Schall U, Campbell LE. Divergent patterns of social cognition performance in autism and 22q11.2 deletion syndrome (22q11DS). J Autism Dev Disord. 2013;43:1926-34.
38. Antshel KM, Fremont W, Ramanathan S, Kates WR. Predicting cognition and psychosis in young adults with 22q11.2 Deletion Syndrome. Schizophrenia Bull. 2017;43(4):833-42.
39. Badoud D, Schneider M, Menghetti S, Glaser B, Debbané M, Eliez S. Understanding others: a pilot investigation of cognitive and affective facets of social cognition in patients with 22q11.2 deletion syndrome (22q11DS). J Neurodev Disorders. 2017;9:35.