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 Interference 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.

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 phenotypic 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, ioparathyroidism [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 psychotonic 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...
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 Di-George 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 tests were corrected for multiple comparisons. For categorical variables χ2 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 IQ 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 (X2 = 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 IQ 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>CS (n = 30)</th>
<th>SIB (n = 20)</th>
<th>SCZ (n = 39)</th>
<th>DEL_scz (n = 17)</th>
<th>DEL (n = 34)</th>
<th>Statistics</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Sex (%)</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>χ2</td>
<td>p</td>
</tr>
<tr>
<td>Age (mean ± sd)</td>
<td>28.9 ± 7.5</td>
<td>42.7 ± 12.9</td>
<td>35 ± 9.9</td>
<td>27.5 ± 6.7</td>
<td>24.3 ± 6.9</td>
<td>F = 16.183</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>IQ (mean ± sd)</td>
<td>113.5 ± 10.8</td>
<td>99.4 ± 8.8</td>
<td>90.4 ± 18</td>
<td>82.5 ± 19.6</td>
<td>89.1 ± 15.1</td>
<td>F = 16.854</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>PANSS pos</td>
<td>13.4 ± 4.2</td>
<td>14.2 ± 6.1</td>
<td>t = -0.525</td>
<td>0.602</td>
<td></td>
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<tr>
<td>PANSS neg</td>
<td>20.1 ± 7.3</td>
<td>16.8 ± 6</td>
<td>t = 1.637</td>
<td>0.107</td>
<td></td>
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<tr>
<td>PANSS gen</td>
<td>35.2 ± 8.1</td>
<td>32.3 ± 8.9</td>
<td>t = 1.087</td>
<td>0.282</td>
<td></td>
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<tr>
<td>DoIr (mean ± sd)</td>
<td>106 ± 8</td>
<td>7.1 ± 5</td>
<td>t = 1.33</td>
<td>0.187</td>
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</tbody>
</table>

CS: control subjects; SIB: siblings of schizophrenic patients; SCZ: schizophrenics; DEL_scz: psychotic patients; DEL: non psychotic patients. Std: 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 = 6.245; p < 0.001; partial Eta2 = 0.159); negative emotions (F = 8.2017; p < 0.001; partial Eta2 = 0.199); emotion recognition (F = 10.258; p < 0.001; partial Eta2 = 0.237); sincere (F = 3.224; p = 0.015; partial Eta2 = 0.089); simple sarcasm (F = 11.081; p < 0.001; partial Eta2 = 0.251); paradoxical sarcasm (F = 17.495; p < 0.001; partial Eta2 = 0.346); social inference (minimal) (F = 17.945; p < 0.001; partial Eta2 = 0.352); sarcasm enriched (F = 5.779; p < 0.001; partial Eta2 = 0.149); lie (F = 10.9; p < 0.001; partial Eta2 = 0.248); social inference (enriched) (F = 15.853; p < 0.001; partial Eta2 = 0.325). Age showed a significant effect on the following TASIT scales: paradoxical sarcasm (F = 4.166; p = 0.043; partial Eta2 = 0.031); social inference (minimal) (F = 5.199; p = 0.024; partial Eta2 = 0.038); sarcasm enriched (F = 6.903; p = 0.010; partial Eta2 = 0.050). IQ presented a significant effect on the following TASIT scales: positive emotions (F = 6.320; p = 0.013; partial Eta2 = 0.046); negative emotions (F = 5.825; p < 0.017; partial Eta2 = 0.042); emotion recognition (F = 9.274; p = 0.003; partial Eta2 = 0.066); simple sarcasm (F = 4.381; p = 0.038; partial Eta2 = 0.032); social inference (minimal) (F = 4.586; p = 0.034; partial Eta2 = 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 SB 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 TASIT 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.
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Strated for 22q11.2 deletion syndrome [36].

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 rehabilitative 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 TASIT 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 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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