Neurocognitive profile and onset of psychosis symptoms in children, adolescents and young adults with 22q11 deletion syndrome: A longitudinal study

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A B S T R A C T

Background: The neurobehavioral phenotype of 22q11.2 deletion syndrome (22q11DS) includes cognitive dysfunction and high rates of psychotic symptoms and schizophrenia. Existing research has mainly considered changes in IQ, especially its decline, as a psychosis predictor. The aim of this study was to investigate, in a longitudinal perspective, the relationship between neuropsychological abilities (not only IQ but also executive functioning, language and visual-motor integration abilities) and onset of psychotic symptoms in a sample of children, adolescents and young adults with 22q11DS.

In addition, the role of comorbid psychiatric disorders at baseline was taken into account.

Methods: 75 participants with 22q11DS, aged between 6 and 27 years at baseline, were included. Eighteen of the 75 participants had developed psychosis at the one year follow-up (onset psychosis-OP) and constituted the first group; 57 participants who had not developed a psychosis at the one year follow-up (without onset psychosis-WOP) constituted the second group.

Results: At baseline, group OP showed lower IQ (both full scale and verbal and performance scale) and more perseverative errors as well as a reduced number of correct categories on the Wisconsin Card Sorting Test (WCST) compared to group WOP. In addition, at baseline, group OP showed a higher frequency of depressive disorders than group WOP.

Conclusion: Even if with caution, results suggest neuropsychological deficits and depressive symptoms should be considered and monitored as possible clinical signs for the onset of psychosis in children, adolescents and young adults with 22q11DS.

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1. Introduction

22q11.2 deletion syndrome (22q11DS), originally known as velocardiofacial syndrome or DiGeorge syndrome, is a genetic syndrome (Schneider et al., 2014a; Scambler et al., 1992) associated with microdeletion of the chromosome 22 band q11 with an estimated prevalence varying between 1 per 3000 to 1 per 6000 live births (McDonald-McGinn and Sullivan, 2011). The physical and neurobehavioral phenotype of the syndrome includes high rates of congenital dysmorphic features (Bassett et al., 2001; McDonald-McGinn and Sullivan, 2011), structural brain abnormalities (Chow et al., 1999), cognitive dysfunction (Vorstman et al., 2015; Antshel et al., 2010), and high rates of psychiatric disorders (Gothelf et al., 2008), in particular schizophrenia (Murphy, 2005; Schneider et al., 2014a).

The cognitive profile in individuals with 22q11DS varies over the course of development and is highly variable between individuals (Schneider et al., 2014a; Armando et al., 2013). However, there are some replicated patterns. The majority of individuals with 22q11DS have an intellectual ability that falls in the borderline range (IQ 70–84), about one-third present mild intellectual disability, while more severe intellectual disability is uncommon (Bassett et al., 2005; Chow et al., 2006; Swillen et al., 2000). In early childhood, children with 22q11DS show non-verbal learning deficits and performance IQ tends to be significantly lower than verbal IQ (De Smedt et al., 2009; Jacobson et al., 2010; Swillen et al., 1999). However, data seem do not support the distinction between performance and verbal IQ scores in adolescence (Antshel et al., 2010; Green et al., 2009).

Concerning predictive factors of later psychotic onset in individuals with 22q11DS, the IQ, and specifically its decline, is one of the most reliable predictors of subsequent psychotic onset (Kates et al., 2015; Vorstman et al., 2015). Indeed, results of three longitudinal studies examining the period of late childhood and adolescence to adulthood documented that individuals with 22q11DS developing psychosis show a
gradual cognitive decline as they enter into adulthood (Gothelf et al., 2005; Antshel et al., 2010; Vorstman et al., 2015).

More specifically, in a prospective longitudinal cohort study, Vorstman et al. (2015) included 411 individuals with 22q11DS (mean age: 16.1 (sd: 6.2)) with at least two IQ measurement at age 8–24 years. All patients showed a decline in IQ over time, particularly in Verbal IQ. The average total declines in cognitive abilities were 7.04 points in Full Scale IQ, 9.02 points in Verbal IQ, and 5.09 points in Performance IQ. Even more interesting, Vorstman et al., 2015 found that cognitive decline (Full scale IQ and both scales with most pronounced for Verbal IQ) was greater in individuals with 22q11DS who develop a psychotic disorder, and this decline appears to start as early as age 11 years. Overall, based on Vorstman et al., 2015, individuals with 22q11DS who develop psychotic disorder show a significant cognitive decline that is significantly steeper than the intellectual decline over childhood and adolescence observed in individuals with 22q11DS without psychosis.

Existing research has mainly considered changes in IQ as a psychosis predictor in 22q11DS, but very little research has considered other neuropsychological domains as possible predictors. In the latter context, Schneider et al. (2014b) carried out a longitudinal study (3 years between two time points) on the associations between neuropsychological profile and psychotic symptoms in a group of 56 adults with 22q11DS. The results showed that, in several neuropsychological domains (full-scale IQ, processing speed, and verbal memory), individuals with 22q11DS and psychotic symptoms were significantly more impaired than those without psychotic symptoms. However, the study by Schneider et al. (2014b) included some adults with 22q11DS who showed psychiatric disorders in comorbidity. As the authors underlined, this may have increased the prevalence of psychiatric disorders in a group of 56 adults with 22q11DS and, since the follow-up started in adulthood, the conclusions must not be considered definitive. More recently Antshel et al. (2017) examined the extent to which the developmental trajectories of cognitive abilities, academic abilities, executive functioning, attention, working memory, and emotion recognition can be predictive of psychosis in young adults with 22q11DS. Eighty-two children and adolescents with 22q11DS were assessed for psychiatric disorders and neuropsychological functioning at 4 time points, with approximately 3 years between time points. Results showed that visual and auditory working memory abilities and academic abilities improved at a slower rate for individuals with 22q11DS than those without psychosis. More interestingly, perseverative error scores in the Wisconsin Card Sorting Test and thus, cognitive flexibility, were robust predictors of prodromal/overt psychotic symptoms in adulthood. Indeed, individuals with 22q11DS who developed prodromal/overt psychotic symptoms continued to demonstrate deficits in cognitive flexibility and improved less appreciably than individuals with 22q11DS who did not show prodromal/overt psychotic symptoms. However, the study by Antshel et al. (2017) has the limitation that longitudinal assessments were conducted every 3 years, and the possibility should be considered that changes may have occurred earlier and that developmental progression of psychotic symptoms was not detected. In addition, medication history was not controlled for. Medication may have reduced some psychotic symptoms and affected the results concerning the neuropsychological performance. Finally, the authors did not clarify the distribution of psychiatric co-morbidities amongst the patients.

The aim of the present study was to investigate, in a longitudinal perspective, the relationship between neuropsychological abilities and the onset of psychotic symptoms in a group of children, adolescents and young adults with 22q11DS. The follow-up time (12 months) in our study was shorter than that of previous studies in order to assess early changes in the clinical course of 22q11DS; furthermore, not only general cognitive abilities but also executive functioning, language (lexical comprehension) and visual-motor integration abilities were fully investigated.

In addition, the possible effects of pharmacological treatments were taken into consideration when examining the relationship between neuropsychological abilities and onset of psychotic symptoms in individuals with 22q11DS. Finally, besides psychotic symptoms, other comorbid psychiatric disorders in individuals with 22q11DS who develop psychosis and in those who do not develop psychosis were taken into account at baseline.

2. Methods

2.1. Participants

Seventy-five participants (31 females, 44 males) with a genetically confirmed 22q11DS diagnosis, aged between 6 and 27 years (14.6 ± 5.1 years) at baseline (T0), were included in the study. Participants were recruited from the Child and Adolescent Neuropsychiatry Unit and the Clinical Genetic Unit of the Bambino Gesù Clinical and Research Hospital in Rome between 2014 and 2016. They were identified by standard cytogenetic studies using fluorescence in situ hybridisation (FISH; O’Connor, 2008) and a probe from the commonly deleted 22q11.2 region.

Participants were assessed from 6 years of age onwards, due previous reports in which the presence of psychotic symptoms in individuals with 22q11DS was also documented in school-aged children (Debbané et al., 2006). Participants were followed-up over a mean period of 12 months.

Interval time between T0 and T1 ranged from 8 months to 16 months. The exclusion criterion was having a psychotic disorder or positive psychotic symptoms at baseline or before the first evaluation at our service.

The study was approved by Ethics Committee of the Bambino Gesù Clinical and Research Hospital in Rome and was conducted in agreement with the Italian Association for 22q11DS microdeletion syndrome (Aidel22) in the framework of a wider project aimed at the prevention of psychopathological disorders in patients with 22q11DS. All participants provided written informed consent and parental consent for those under 18 years of age. The 75 participants were divided into two groups based on the onset of psychosis at the one-year follow-up. Onset of psychosis was diagnosed in individuals with 22q11DS presenting a score of 6 in at least one item positive for SIPS/SOPS (see paragraph on Clinical Assessment for this instrument).

The first group of participants with 22q11DS who had developed psychosis (onset psychosis - OP) at one-year follow-up (T1) consisted of 18 participants (9 females, 9 males); the second group who had not developed psychosis (without onset psychosis - WOP) consisted of 57 participants (20 females, 37 males).

The groups with OP and WOP differed significantly in terms of chronological age (OP: 18.06 ± 5.1 years; WOP: 13.5 ± 4.6 years; p = 0.0016 Mann-Whitney).

2.2. Measures

2.2.1. Clinical assessment

The Structured Interview for Psychosis-Risk Syndromes (SIPS/SOPS; McGlashan, 2001) was administered to all participants at T0 and T1 by a trained psychiatrist during the structured psychiatric interview. The SIPS scales include a total of 19 symptom constructs (five positive, six negative, four disorganized and four general symptoms) that are evaluated based on the presence, duration and severity of specific experiences and behavior. Each item is rated on a scale of 0 (symptom absent) to 6 (extreme or psychotic symptom intensity).

The SIPS/SOPS contains diagnostic criteria for three ‘psychosis risk syndromes’: attenuated psychotic symptoms (APS), brief limited intermittent symptoms (BLIPS), schizotypal personality disorder (according to the diagnostic criteria of the DSM-IV) and psychosis (score equal to 6 in any of the five positive items).
At T0 and T1, the presence of any Axis I DSM-IV psychiatric disorder was assessed using structured clinical interviews. The Structured Clinical Interview for Axis I DSM-IV (SCID-I) was administered to adult participants and their parents.

For participants under 18 years and their parents, the Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) was administered.

For the Global Assessment of Functioning, the Childhood Global Assessment Scale (Shaffer et al., 1993) or the Global Assessment of Functioning (from DSM-IV-TR, American Psychiatric Association, 2000) was used.

2.2.2. Neuropsychological assessment

All participants completed the neuropsychological assessment. IQ was assessed using the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991) or the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) which provides scores for Verbal IQ, Performance IQ, and Full Scale IQ.

Lexical comprehension was evaluated using the Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn, 1981) which provides age-specific standard scores (with a mean of 100 and standard deviation of 15).

The Visual Motor Integration Task (VMI; Beery and Buktenica, 1997) was used to measure visual-motor integration.

Raw scores were converted into percentiles. The latter were considered for the analyses.

The Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) was used to assess categorization and perseveration. The total number of perseverative errors (raw scores were converted into age-specific standard scores) and the number of categories were considered for the analyses.

The Stroop task (Stroop, 1935) was used to evaluate verbal response inhibition. Index interference was considered for the analyses. As an index of interference, we considered the difference relative to the baseline in execution time, computed as [(incongruent-control)/control], where the control is the second neutral condition (to read a list of color words printed in black) and incongruent is the condition in which the color words are printed in a different color (e.g. “blue” printed in red).

Two different tasks were used to test verbal fluency. The phonological task (FAS; Marotta et al., 2008) was used to assess phonemic verbal fluency (i.e. F, A, S). Specifically, participants were asked to produce as many words as they could beginning with each phoneme in 60 s. The categorical task (CAT; Vicari, 2007) assesses semantic fluency. Participants were asked to recall as many words as possible in each category (animals, fruit, clothing and toys) in 60 s. The total number of items correctly recalled is recorded for FAS and CAT (for both tasks, raw scores were converted into age-specific percentiles).

To assess verbal category shifting, CAT alternate was used (Mäntylä et al., 2007). Participants were asked to produce words that shift between two categories (i.e. animals and fruits). The score was calculated on the basis of the number of correctly generated pairs within 120 s. Raw scores were considered for the analyses due to the lack of normative data for this task.

2.3. Statistical analyses

As not all neuropsychological variables met homoscedasticity assumptions (the Levene’s test showed significant differences in variance), the Mann–Whitney U test was used to compare, at T0, participants with 22q11DS who developed psychosis at one-year follow-up and those who did not.

Since several neuropsychological measures were considered (full scale IQ, verbal IQ, performance IQ, PPVT, WCST category, WCST perseverative errors, FAS, CAT, CAT alternate, STROOP, and VMI) and separate analyses could produce alpha-inflation (increase of false positive findings), statistical significance was adjusted for the number of tests performed (Bonferroni adjustments 0.05/11 = 0.0045).

Statistical analysis was performed using Statistica 10 (StatSoft, Tulsa, OK).

3. Results

3.1. Neuropsychological differences at T0

As shown in Table 1, the groups with OP and WOP did not differ at T0 in lexical comprehension (PPVT: p = 0.98 Mann-Whitney) and in visuo-motor integration (VMI: p = 0.41 Mann-Whitney) skills. Even if groups did not differ on VMI, only patients with OP showed a mean score below the fifth percentile. They also did not differ in verbal fluency abilities (CAT: p = 0.68 Mann-Whitney; FAS: p = 0.83 Mann-Whitney), in verbal category shifting (CAT alternate: p = 0.29 Mann-Whitney), and in verbal response inhibition (STROOP: p = 0.61 Mann-Whitney).

However, the two groups with 22q11DS differed in IQ (Full Scale IQ: p = 0.001 Mann-Whitney; Verbal IQ: p = 0.002 Mann-Whitney; Performance IQ: p = 0.001 Mann-Whitney), in perseverative errors (p = 0.00002 Mann-Whitney) and in category numbers (p = 0.00004 Mann-Whitney) on WCST. Specifically, at T0 participants with OP showed more perseverative errors and a reduced number of categories on WCST compared to participants in the WOP group.

3.2. Age effect on neuropsychological differences at T0

To show that the neuropsychological differences found between OP and WOP participants were not related to differences in age (the WOP group was significantly younger than the OP group), younger children from the WOP group were excluded to match the group with OP for chronological age. A subgroup of 28 participants was then selected (17.1 ± 3.58 years) from the whole WOP group and matched for chronological age (p = 0.46 Mann-Whitney) with the OP group of participants (18.1 ± 5.1 years).

Statistical analyses confirmed our previous results (with the older WOP group), showing that participants with OP had a lower IQ (Full Scale IQ: p = 0.0008 Mann-Whitney; Verbal IQ: p = 0.0006 Mann-Whitney; Performance IQ: p = 0.0006 Mann-Whitney) than the WOP group, made more perseverative errors (p = 0.0003 Mann-Whitney), and completed a reduced number of categories (p = 0.0002 Mann-Whitney) on WCST. Similarly to our previous analyses on the whole groups, there was no difference between the OP group and the WOP subgroup for the other neuropsychological measures considered

Table 1

<table>
<thead>
<tr>
<th>Neuropsychological measures at T0</th>
<th>OPa (n = 18)</th>
<th>WOPb (n = 57)</th>
<th>CA WOPa (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Full scale IQ</td>
<td>75.61 ± 9.32</td>
<td>86.1 ± 11.50</td>
<td>87.2 ± 9.49</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>75.94 ± 10.82</td>
<td>86.4 ± 11.55</td>
<td>87.9 ± 9.57</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>76 ± 10.31</td>
<td>86.6 ± 11.47</td>
<td>87.9 ± 9.44</td>
</tr>
<tr>
<td>STROOP</td>
<td>48 ± 25.42</td>
<td>38.6 ± 8.86</td>
<td>34.0 ± 8.16</td>
</tr>
<tr>
<td>WCST (categories)</td>
<td>2.39 ± 1.42</td>
<td>4.3 ± 1.53</td>
<td>4.5 ± 1.60</td>
</tr>
<tr>
<td>WCST (perseverative errors)</td>
<td>77.56 ± 21.32</td>
<td>106.8 ± 105.3</td>
<td>121.32 ± 22.41</td>
</tr>
<tr>
<td>PPVT</td>
<td>83.08 ± 11.34</td>
<td>83.9 ± 14.33</td>
<td>86.1 ± 14.02</td>
</tr>
<tr>
<td>FAS</td>
<td>26 ± 19.66</td>
<td>26.6 ± 19.45</td>
<td>23.1 ± 18.26</td>
</tr>
<tr>
<td>CAT</td>
<td>3 ± 3.96</td>
<td>4.8 ± 10.12</td>
<td>5.8 ± 12.80</td>
</tr>
<tr>
<td>CAT alternate</td>
<td>7 ± 4.02</td>
<td>6.4 ± 3.01</td>
<td>6.5 ± 3.38</td>
</tr>
<tr>
<td>VMI</td>
<td>4 ± 5.99</td>
<td>12 ± 21.82</td>
<td>7 ± 14.93</td>
</tr>
</tbody>
</table>

a OP = participants with onset of psychosis at the one-year follow-up.
b WOP = participants without onset of psychosis at the one-year follow-up.
c CA WOP = WOP matched for chronological age with OP.
(PPTV, VMI, CAT, FAS, CAT alternate and STROOP) \( (p \text{ always } >0.1 \text{ Mann-Whitney}) \).

3.3. Psychiatric diagnosis at T0

Percentage frequencies of current Axis I disorders at T0 were calculated for total group and separately for the two groups (Table 2). As can be seen, at T0, the group with OP showed higher frequency of depressive disorders than the WOP group. This result was confirmed by \( \chi^2 \text{ test} (\chi^2 = 11.20; \text{p-value}: <0.01) \).

3.4. Medication effect on relationship between cognitive deficit and onset of psychotic symptoms

In both groups, at T0, no patients were taking drugs and had not received drugs during the 12-months prior to follow-up. For the group with OP, pharmacological treatment was started immediately after the detection of psychotic symptoms during the follow-up assessment.

4. Discussion

The main aim of present study was to explore, in a longitudinal perspective, the relationship between neuropsychological abilities and the onset of psychotic symptoms in a group of children, adolescents and young adults with 22q11DS.

The first result we obtained was that, at baseline level, participants with 22q11DS who had developed psychosis at one-year follow-up (OP group) had lower IQ (both full and verbal and performance scale) than participants who had not developed psychosis (WOP group). This finding is in line with previous studies carried out on individuals with 22q11DS (Schneider et al., 2014b; Vorstman et al., 2015; Antshel et al., 2017) as well as on general populations, where low IQ increases the risk for many neuropsychiatric disorders in general (Gale et al., 2008; Koenen et al., 2009; Dekker et al., 2002) and particularly for psychosis (Woodberry et al., 2008; Zammit et al., 2004).

More recently, in a prospective cohort study included 4322 participants, Mollon et al. (2018) showed that individuals with psychotic disorder had large and increasing IQ deficits (both verbal and nonverbal abilities) as well as slowed developmental growth in specific cognitive functions, such as working memory.

Secondly, at baseline level, participants with 22q11DS who had developed psychosis at-one-year follow-up (OP group) showed a higher level of impairment in executive functions as assessed with WCST. Namely, participants with OP showed more perseverative errors and a reduced correct number of categories on WCST compared to WOP participants. These results indicate that the performance obtained on WCST by our patients with 22q11DS at T0 is a crucial marker for the onset of psychotic symptoms as measured by the scores at positive items of SIPS/SOPS at one-year follow-up. Present findings are consistent with those reported in the study by Antshel et al. (2017) which showed that individuals with 22q11DS who developed psychotic symptoms improved less appreciably and continued to demonstrate difficulties with cognitive flexibility as assessed with WCST compared to individuals with 22q11DS who did not have psychotic symptoms.

It is noteworthy that baseline executive function deficits assessed with WCST are also associated with psychosis diagnosis at follow-up in the general population (Remberk et al., 2014).

The low performance on WCST is the only measure of executive functioning that precedes the onset of psychotic symptoms. Indeed, in our study we also examined performance on the Stroop test, CAT and FAS and found no significant differences between the group with OP and the WOP group. This result is supported by the standard score of perseverative errors on WCST that was below the mean in the OP group and in the normal range in the WOP group. The cognitive flexibility, attention shifting and set maintenance deficit (as measured by WCST) could thus be a key feature for identifying individuals with 22q11DS at risk for developing psychosis. Conversely, response inhibition (measured by Stroop) and verbal fluency (measured by CAT, CAT shifting and FAS) are less associated with the psychiatric outcome. This finding is consistent with that of Maeder et al. (2016) who found that deficit in response inhibition and verbal fluency preceded the onset of negative symptoms but not of positive symptoms. However, further studies are needed to investigate the relationship between specific deficits in executive functioning and the dimensions of psychotic symptomatology in individuals with 22q11DS (positive, negative, disorganization, and general).

Indeed, in individuals with 22q11DS, in idiopathic schizophrenia or in high-risk populations, negative and cognitive psychotic symptoms may be a more useful outcome variable, as they may be a better “predictor” of full-blown schizophrenia and at least have been reported to have more significant and long-lasting impact on daily-life functioning (Carbon and Correll, 2018; Basso et al., 1998).

In our study, the follow-up for psychiatric assessment was twelve months after the neuropsychological evaluation. In our opinion, this is a correct interval for detecting changes in the psychiatric status. Indeed, a longer interval could increase the risk of not detecting the onset of the psychotic symptoms and, consequently, the loss of information on neuropsychological deficits and the next onset of psychotic symptoms.

Since all the participants in the two groups were drug naive, changes in psychiatric status documented in the present study are not related to the effects of possible pharmacological treatments. In previous studies on the relationship between neuropsychological and psychiatric profiles (Schneider et al., 2014a; Antshel et al., 2017) potential pharmacological effects were not investigated.

Matching the participants in the OP and WOP groups for chronological age confirmed the present findings and showed that our results did not depend on differences in age. Specifically, at baseline, participants with 22q11DS who will develop a psychosis at the one-year follow-up showed lower abilities in IQ (full, verbal and performance) and in specific executive functions (cognitive flexibility, attention shifting and set maintenance measured by WCST) compared with aged-matched participants with 22q11DS who will not develop a psychosis. Present findings are in keeping with other studies that have explored the association between cognitive deficits and psychosis vulnerability in individuals with 22q11DS and in general population.

Specifically, executive functioning, attention and working memory are often impaired in 22q11DS (Shapiro et al., 2014) and predictive for psychosis in idiopathic schizophrenia (Meier et al., 2014; Comblatt et al., 1998). Moreover, research on cognitive abilities in schizophrenia indicates that cognitive decline occurs in late adolescence (Woodberry et al., 2008) although academic and cognitive deficits could also be found in children who later develop schizophrenia (Cannon et al., 2002; Jones et al., 1994).

Overall, our results suggest that the neuropsychological deficits could be considered a marker for psychosis vulnerability in individuals with 22q11DS and are aspects to consider in the clinical assessment and management of children, adolescents and young adults with this syndrome.

Furthermore, at baseline level, we considered differences in psychiatric comorbidity between the two groups to evaluate the relationship

| Table 2 Percentage frequencies of current Axis I disorders at T0 calculated for total group and separately for the two groups. |
|-----------------|-----------------|-----------------|
| Mood disorder (%) | Anxiety disorder (%) | Behavioural disorder (%) |
| Total group (n = 75) | 36 (49) | 24 (31) | 15 (20) |
| OP (n = 18) | 12 (67) | 4 (22) | 2 (11) |
| WOP (n = 57) | 25 (44) | 19 (33) | 13 (23) |
between other psychiatric risk factors and the onset of psychosis in individuals with 22q11DS. The group with OP showed significantly higher frequency of depressive disorders than the WOP group. Therefore, at least in our participants, the presence of depression precedes the onset of psychotic symptoms at one-year follow-up. This finding is in contrast to the findings of a previous study (Gothelf et al., 2007) showing that anxiety symptoms are psychiatric risk factors for psychosis. Indeed, in the study by Gothelf et al. (2007) participants with 22q11DS are younger (12.9 years) than those of our group with OP (17.7 years), and since depressive symptoms are more frequently documented in older patients (Schneider et al., 2014a), we retain that the age difference between the participants of the two studies may explain the contrary findings. Consistent with Schneider et al. (2014b), in 22q11DS the prevalence of anxiety disorders decreases with age (decreasing from 35% in the 6–12 years age group to 24% in the 18–25 years age group) while that of depressive disorders increases (from 3% in the 6–12 age group to 18% in the 18–25 age group). However, as already pointed out by authors as limitation of the study (Schneider et al., 2014b), discrepancies between the age groups could be partially explained by diverse assessment employed by the different sites that contributed to the data. However, as already pointed out by authors as limitation of the study (Schneider et al., 2014b), discrepancies between the age groups could be partially explained by diverse assessment employed by the different sites that contributed to the data. Thus, although the findings by Schneider et al. (2014b) should be considered with caution, they are in line with our results since in older participants the relation of depressive symptoms with the onset of psychosis is more prevalent than in the study by Gothelf et al. (2007). A further possible explanation is that, by documenting depressive symptoms one year before the psychosis onset, we were looking at negative symptoms of the psychosis. Indeed, up to 80% of patients with 22q11DS present attenuated negative symptoms (Schneider et al., 2012) and, in the prodromal psychotic phase, attenuated negative symptoms have a higher prevalence than positive symptoms (Challis et al., 2011). In light of this, a limitation of our study is not having evaluated with a specific instrument the negative symptomatology in patients with 22q11DS.

Overall, this is one of the first longitudinal studies investigating the relationship between neuropsychological abilities and the onset of psychosis in patients with 22q11DS taking into account the effects of age, psychiatric comorbidity and pharmacological treatment.

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Contributors
Authors Maria Pontillo and Stefano Vicari designed the study and wrote the protocol. Author Deny Menghini and Stefano Vicari undertook the statistical analysis and all authors contributed to the first draft and all authors contributed to and have approved the final manuscript. Author Maria Pontillo is first authorship and the corresponding author.

Conflict of interest
There are no conflicts of interest of any of the authors including any financial, personal or other relationships with other people or organizations that could inappropriate influence, or be perceived to influence, our work.

References
Carbon, M., Correll, CU, 2018. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectr. 19 (1), 38–52.