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Prevalence, course and psychosis-predictive value of negative symptoms in 22q11.2 deletion syndrome

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ABSTRACT

Background: The 22q11.2 deletion syndrome (22q11DS) is one of the highest known risk factors for schizophrenia and recent findings have highlighted the clinical relevance of ultra-high risk (UHR) criteria in this population. However, studies in other at-risk populations have shown that the presence of negative symptoms (NS) is also of clinical relevance in predicting transition to psychosis. The present study examined in detail the presence and course of NS in 22q11DS, as well as their value in predicting transition to psychosis.
Methods: A total of 111 participants aged between 8 and 33 years were assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS). A follow-up assessment was available for 89 individuals.
Results: Core NS of at least moderate severity were present in 50.5% of the sample and were more severe in individuals meeting UHR criteria. They predominantly remained stable over time and their emergence between baseline and follow-up assessment was associated with significant functional decline. Some NS were significant predictors of conversion to psychosis and the emergence/persistence of psychosis risk.
Conclusions: Altogether, these findings highlight that NS are core manifestations of psychosis in individuals with 22q11DS that strongly impact global functioning. The presence of NS should be a primary target of early therapeutic intervention in this population.

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1. Introduction

The 22q11.2 deletion syndrome (22q11DS) is the most common microdeletion in humans, with an incidence varying between 1/2000–4000 live births and up to 1/1000 pregnancies (Grati et al., 2015; Oskarsdóttir et al., 2004), and is one of the highest known risk factors for schizophrenia (Murphy and Owen, 2001). According to Murphy and Owen (2001), only offspring with two parents diagnosed with schizophrenia or individuals with a monozygotic twin affected by schizophrenia have a higher risk to develop this condition. While 23% to 45% of adolescents with 22q11DS report transient psychotic experiences (Armando et al., 2012; Debbané et al., 2006; Schneider et al., 2012; Shapiro et al., 2011; Stoddard et al., 2010), between 20% and 40% (depending on study design and referral source) of affected adults are diagnosed with a psychotic disorder (Schneider et al., 2014a). Thus, the detection of patients with 22q11DS at particularly high risk of conversion to psychosis is crucial to improve early diagnosis and treatment in this population. Today, the ultra-high risk (UHR) criteria are one of the most frequently used clinical tools to identify individuals at clinical high-risk (CHR) for psychosis in clinical samples (Fusar-Poli et al., 2015; Schultze-Lutter et al., 2015). These criteria mostly focus on the presence of positive psychotic manifestations meeting certain frequency and onset/worsening requirements. The validity of UHR criteria in predicting transition to psychosis has been recently established in participants with 22q11DS, with a transition rate of 27.3% over a 32-month interval (Schneider et al., 2016). Despite the clinical relevance of these criteria in 22q11DS, the rates of false negatives (4.5%) and of remission from a UHR condition (45.5%) were as high as those observed in other at-risk samples (Fusar-Poli et al., 2015; Michel et al., 2018; Schultze-Lutter et al., 2015). This stresses

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the need to combine UHR criteria with additional risk factors for psychosis also in this genetic high-risk group.

Recent findings in individuals at CHR for psychosis have shown that the presence of negative symptoms (NS) is also of clinical relevance in predicting transition to psychosis (Fusar-Poli et al., 2013; Nelson et al., 2013; Piskulic et al., 2012). In a previous longitudinal study that examined the overall severity of NS as an additional predictor of conversion to psychosis in 22q11DS (Schneider et al., 2016), the statistical significance threshold was just missed (hazard ratio = 1.13, $p = 0.061$). Yet, a summary examination of NS might have failed to detect the predictive value of certain single NS that are generally not considered as a unitary construct (Blanchard et al., 2011; Schneider et al., 2012). Furthermore, a recent study showed that the severity of a baseline composite score including NS and general symptoms was higher in individuals with emergent positive symptoms between baseline and follow-up compared to stable non-psychotic individuals (Tang et al., 2017). These findings indicate that NS might represent an important additional predictor of conversion to psychosis in 22q11DS.

Cross-sectional studies of single NS assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS; McGlashan et al., 2010) in 22q11DS reported a prevalence of at least any one NS of moderate to extreme severity of about 75% (Schneider et al., 2012; Stoddard et al., 2010). However, this overall prevalence might be overestimated due to the inclusion of items that are not part of the narrow definition of NS, such as Ideational Richness or Occupational Functioning (Kirkpatrick et al., 2006). In light of the high prevalence of NS in 22q11DS, prominent NS might represent a clinical characteristic of the 22q11DS phenotype. Supporting this view, two studies reported that NS were more severe in individuals with 22q11DS compared to other psychosis-risk samples (Armando et al., 2012; Shapiro et al., 2011). In addition, approximately a third of individuals with 22q11DS were shown to have predominant NS in the absence of (attenuated) positive symptoms (Schneider et al., 2014b). Yet, for the lack of knowledge of the development of NS in relation to positive symptoms in 22q11DS, it remains unclear if NS might herald the future occurrence of positive symptoms or characterize a different subgroup of individuals.

To shed light on the unclear, yet possibly crucial role of NS in 22q11DS, the present study examined the presence and course of NS assessed with the SIPS in a large sample from two different cohorts (Armando et al., 2017; Schneider et al., 2016). At the cross-sectional level, the prevalence and factor structure of NS as well as their severity and prevalence in relation to the presence of UHR criteria were examined. Based on findings in other UHR samples (Fusar-Poli and Borgwardt, 2007; Piskulic et al., 2012), we expected more frequent and severe NS in 22q11DS participants meeting UHR criteria. At the longitudinal level, we examined the course of NS over a 32-month interval (i.e. presence and severity of NS at baseline and follow-up) in relation to baseline and change in general functioning, persistence/onset of UHR condition at follow-up, and transition to psychosis at follow-up. Significant associations between the presence of single NS at baseline and transition to psychosis, as well as the presence of a UHR condition at follow-up were expected.

2. Methods

2.1. Sample

We included 111 participants (81 from Geneva and 30 from Rome; see Table S1 for a comparison of the cohorts) with a genetically confirmed 22q11DS diagnosis, aged between 8 and 33 years (M = 15.70, SD = 4.71; 76.6% being below 18 years of age) at baseline. At baseline, 13 (11.7%) participants received methylphenidate, 7 (6.3%) antipsychotics, 5 (4.5%) antidepressants, 2 (1.8%) mood stabilizers, and 1 (0.9%) anxiolytics. Participants of the Geneva cohort were recruited though advertisements in patient associations or word of mouth. Participants of the Rome cohort were referred from the Genetic Clinical Unit of the Bambino Gesu Hospital and through advertisement in patient associations. Written informed consent from the participants and their parents was collected at both sites under protocols approved by local Institutional Ethical Review Boards.

Eighty-nine participants (80.2% of the total sample) underwent a follow-up assessment (see Table S2 for a comparison of the participants with and without a follow-up assessment available). The mean follow-up period was 32.5 months (SD = 17.6; range: 12–85). The mean age at follow-up was 16.08 years (SD = 4.72; range: 9–30 years). Four participants declined to participate to the follow-up assessment and one family could not be located after the initial assessment. At the time of data analysis, 17 participants had not been asked to participate to the follow-up assessment yet because the minimal time interval between the two assessments had not been reached.

2.2. Assessments

All participants were interviewed with the SIPS to assess the severity of positive, negative, disorganization, and general symptoms on a 7-point scale ranging from '0' (absent) to '6' (extreme/severe and psychotic), as well as the presence of UHR criteria (i.e. attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), or Genetic Risk – defined by a first-degree relative with psychosis or presence of a schizotypal personality disorder – and Functional Decline (GRFD) criteria).

For the global assessment of functioning, the Childhood Global Assessment Scale (CGAS; Shaffer et al., 1983) and the Global Assessment of Functioning (GAF) was used. Both scales have been reported to lead to similar results (Schorre and Vandvik, 2004).

The presence of any axis-I psychotic disorder was assessed at both sites using structured clinical interviews. In Geneva, parents of minors completed the Diagnostic Interview for Children and Adolescents–Revised (DICA-IV; Reich, 2000) and the psychotic disorders supplement of the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997). In Rome, only the K-SADS-PL was used in children and adolescents below 18 years. In both cohorts, the Structured Clinical Interview for Axis I DSM-IV (SCID-I; Spitzer et al., 1992) was administered to adult participants and their parents.

All the measures were collected at baseline and at follow-up (when available).

2.3. Statistical analyses

All statistical analyses were performed using SPSS version 21.

2.3.1. Cross-sectional analyses

An exploratory factor analysis with Promax rotation was first performed to examine the factor structure of NS. Based on a previous study exploring the factor structure of the SIPS in 22q11DS (Schneider et al., 2012), raw SIPS scores of the items only loading on the negative factor (i.e. N1 to N6 and D4) were entered in the factor analysis. Selection of the final factor structure was determined based on the visual exploration of the scree plot and the factors' eigenvalues (>1). To assess the prevalence, NS were considered as present if the item score was ≥3 (i.e. moderate to extreme severity) in accordance with existing definitions (Carrion et al., 2017). The correlation between NS severity and age, as well as the functioning score was examined using Spearman correlations. Finally, both severity and presence of NS was compared between participants with/without a UHR condition using Mann-Whitney U and Chi-square tests, respectively. To determine which NS (either in terms of severity or presence) best predicted the presence of a concurrent UHR condition, all the variables significantly discriminating participants with/without a UHR condition were entered in a stepwise binary logistic regression (using both forward and backward procedure to check for the stability of the results).

2.3.2. Longitudinal analyses

To explore the course of NS over time, the sample was subdivided into 4 groups: absence (absent both at baseline and follow-up; i.e. score < 3 on the SIPS NS at both timepoints), onset (absent at baseline but present at follow-up; i.e. score < 3 on the SIPS NS at baseline but score ≥ 3 at follow-up), remission (present at baseline and absent at follow-up; i.e. score ≥ 3 on the SIPS NS at baseline but score < 3 at follow-up) and persistence (present both at baseline and follow-up; i.e. score ≥ 3 on the SIPS NS at both timepoints). Baseline functioning score and difference between baseline and follow-up functioning was then compared across the 4 groups. Because baseline functioning followed a normal distribution in our sample (Shapiro-Wilk test = 0.985, $p = 0.200$), the group comparison was performed using a single ANOVA with post-hoc Tukey test. The difference score violated normality assumption (Shapiro-Wilk test = 0.960, $p = 0.008$) and was therefore compared across the 4 groups using the Kruskall-Wallis test with post-hoc Bonferroni adjusted pairwise comparisons. Secondly, we used Cox regression analyses in a stepwise approach to determine whether the presence of just any NS or of any specific NS significantly predicted (a) conversion to psychosis, and (b) persistence/onset of psychosis or psychosis risk (i.e. psychosis or UHR condition at follow-up). The interval (in months) between baseline and follow-up assessments was used as time variable in the models. Only dichotomous predictors were included in the model (i.e. presence vs. absence of a given symptom) to increase the clinical significance of the findings. First, each NS was entered individually as a predictor in a series of Cox regression analyses and selected for further analyses when the Wald statistic was significant at a liberal level ($p < 0.15$). This threshold was chosen based on the recommendation of Hosmer and Lemeshow (1999) and has been used in previously published papers (e.g. Fluckiger et al., 2016; Schneider et al., 2016; van Tricht et al., 2014). Next, each selected predictor was entered in a multiple Cox regression analysis, with UHR status always included as predictors. Variables were further selected if the Wald statistic was significant ($p < 0.05$) for both variables (UHR status and NS), indicating that presence of a given NS contributed to the improvement of prediction in the presence of an UHR status. In all regression analyses, a minimum of 5 events per predictor variable was maintained. This ratio was reported to commonly ensure sufficient confidence interval coverage for β1 and the related type I error rate of the test of H0, little bias in the estimate of β1, and thereby sufficient power (Vittinghoff and McCulloch, 2007).

3. Results

3.1. Factor structure

The exploratory factor analysis revealed a clear 2-factor solution based on the eigenvalues and the scree plot. The percentage of explained variance was 56.88% for Factor 1, and 14.96% for Factor 2. Items N2 "Avolition" (factor loading on factor 1, $FL_{F1} = 0.834$), N4 "Experience of Emotions and Self" ($FL_{F1} = 0.780$), N1 "Social Anhedonia" ($FL_{F1} = 0.759$), D4 "Impairment in Personal Hygiene" ($FL_{F1} = 0.697$) and N3 "Expression of Emotions" ($FL_{F1} = 0.632$), loaded ≥0.33 on the first factor that was labeled "Core NS". Items N5 "Ideational Richness" ($FL_{F1} = -0.175$; $FL_{F2} = 1.085$) and N6 "Occupational Functioning" ($FL_{F1} = 0.390$; $FL_{F2} = 0.415$) had higher loadings on the second factor. Only the five "core NS" of the first factor were considered in further analyses because items N5 and N6 do not appear to measure the underlying construct of NS.

3.2. Prevalence of core NS and association with age

Altogether, 56 (50.5%) participants reported the presence of at least one core NS (Table 1). Eighteen each (16.2%) had only one or two NS, eight each (7.2%) three or four NS, and four (3.6%) all five NS. Age had an only small to moderate effect on NS severity (Table 1), and

Table 1
Severity and presence of NS, Spearman correlation of NS severity with age and functioning. Significant correlations are highlighted in **bold** (left part). Comparison of the severity of core NS between participants with and without a concurrent UHR condition. Significant differences are highlighted in **bold** (right part).

	Mean (SD); median severity	N (%) with a severity score of 3–6	Correlation with age	Correlation with functioning	Participants without UHR (N = 81)	Participants with UHR (N = 30)	Mann-Whitney *U* test (*p*-value; Rosenthal r)
					Mean (SD); median severity	Mean (SD); median severity	
Sum score of core NS[a]	8.16 (4.92); 7.00	N/A	**0.221 (p = 0.020)**	**−0.609 (p < 0.001)**	**7.49 (4.67); 7.00**	**9.97 (5.18); 9.50**	**z = 2.406 (p = 0.016; r = 0.23)**
N1 social anhedonia	2.14 (1.33); 2.00	32 (28.8%)	0.170 (p = 0.075)	**−0.512 (p < 0.001)**	**1.94 (1.25); 2.00**	**2.67 (1.42); 2.00**	**z = 2.473 (p = 0.013; r = 0.23)**
N2 avolition	1.95 (1.31); 2.00	40 (36.0%)	0.180 (p = 0.058)	**−0.470 (p < 0.001)**	1.83 (1.26); 2.00	2.30 (1.39); 2.00	z = 1.458 (p = 0.145; r = 0.14)
N3 expression of emotions	2.18 (1.23); 2.00	39 (35.1%)	**0.206 (p = 0.030)**	**−0.416 (p < 0.001)**	2.11 (1.29); 2.00	2.37 (1.07); 2.00	z = 1.233 (p = 0.217; r = 0.12)
N4 experience of emotions and self	1.01 (1.18); 1.00	11 (9.9%)	0.139 (p = 0.147)	**−0.491 (p < 0.001)**	**0.89 (1.16); 0.00**	**1.33 (1.18); 1.00**	**z = 2.066 (p = 0.039; r = 0.20)**
D4 impairment in personal hygiene	0.88 (1.05); 1.00	8 (7.2%)	0.154 (p = 0.107)	**−0.532 (p < 0.001)**	**0.73 (0.90); 0.00**	**1.30 (1.32); 1.00**	**z = 2.210 (p = 0.027; r = 0.21)**

NS = negative symptoms.
[a] Sum score of core NS = (N1 + N2 + N3 + N4 + D4).

correlations with age only became significant in case of the sum of the core NS and N3. All NS were significantly and strongly associated with the global functioning score (Table 1).

3.3. Core NS and UHR criteria

Demographic characteristics of individuals with and without UHR are presented in Table S3. UHR individuals generally showed a higher severity of core NS compared to participants who did not meet UHR criteria (Table 1). Differences became statistically significant for items N1, N4, and D4 as well as for the NS sum score (Table 1). The percentage of participants with at least one NS present was also significantly higher in individuals meeting UHR criteria ($n_{(UHR)} = 20$ (66.7%) vs. $n_{(no\text{-}UHR)} = 36$ (44.4%); $\chi^2 = 4.325$, $p = 0.038$). Yet, this difference became significant only for N1 ($n_{(UHR)} = 14$ (46.7%) vs. $n_{(no\text{-}UHR)} = 18$ (22.2%); $\chi^2 = 6.375$, $p = 0.012$); but not for N2 ($n_{(UHR)} = 13$ (43.3%) vs. $n_{(no\text{-}UHR)} = 27$ (33.3%); $\chi^2 = 0.950$, $p = 0.330$); N3 ($n_{(UHR)} = 11$ (36.7%) vs. $n_{(no\text{-}UHR)} = 28$ (34.6%); $\chi^2 = 0.042$, $p = 0.837$); N4 ($n_{(UHR)} = 4$ (13.3%) vs. $n_{(no\text{-}UHR)} = 7$ (8.6%); $\chi^2 = 0.540$, $p = 0.463$); and D4 ($n_{(UHR)} = 4$ (13.3%) vs. $n_{(no\text{-}UHR)} = 4$ (4.9%); $\chi^2 = 2.307$, $p = 0.129$). All the variables significantly discriminating participants with/without a concurrent UHR condition (sum score of core NS, N1 severity, N4 severity, D4 severity, presence of at least one core NS, and presence of N1) were entered in a stepwise binary logistic regression. N1 severity remained the only significant predictor in the model using both a forward and backward procedure (B = 0.399, $p = 0.013$, Exp (B) = 1.491).

3.4. Course of core NS

Overall, core NS predominately remained stable over time, i.e., persistently absent or present at baseline and follow-up in 73% of cases, their new onset or remission at follow-up only occurring in altogether 12.4–31.5% of cases according to the symptoms (Table 2). Similarly, positive symptoms were either consistently present vs. absent both at baseline and follow-up in 71.9% of the cases. When comparing the affiliation of each participant based on the trajectory of positive and negative symptoms, we observed that 35 (39.3%) individuals were categorized in the same subgroup (i.e. absence, onset, remission, and persistence) for both positive and negative symptoms.

Baseline functioning was compared across 4 groups of participants formed on the basis of the trajectory of NS over time: absence (M = 68.9 (SD = 9.72)), onset (M = 67.1 (SD = 8.37)), remission (M = 59.4 (SD = 6.85)) and persistence (M = 54.6 (SD = 9.21)) of any core NS over time (Fig. 1). There was a statistically significant difference between groups as determined by one-way ANOVA ($F(3,85) = 15.538$, $p < 0.001$). The Tukey post-hoc test revealed that baseline global functioning was significantly higher in the absence group compared to both the remission (diff = 9.53, $p = 0.028$) and the persistence (diff = 14.35, $p < 0.001$) groups. Participants in the onset group also had higher baseline functioning compared to the persistence group (diff = 12.56, $p < 0.001$) but not compared to the remission group (diff = 7.74, $p = 0.171$). Baseline functioning was not significantly different between the absence and onset groups (diff = 1.78, $p = 0.932$), nor between the remission and persistence groups (diff = 4.82, $p = 0.440$).

Change in functioning between baseline and follow-up also revealed significant differences across the four groups ($\chi^2 = 16.567$, $p = 0.001$) (Fig. 1). Post-hoc Bonferroni adjusted pairwise comparisons revealed that functioning was more unstable (i.e. larger difference score) in the onset group compared to the absence ($p = 0.002$), remission ($p = 0.003$) and persistence groups ($p = 0.007$). The other three groups were not significantly different from each other (all $p > 0.05$). By contrast, change in functioning between baseline and follow-up was unrelated to the presence of the UHR condition (i.e. absence at both timepoints; onset between baseline and follow-up; remission from baseline to follow-up; and presence at both timepoints) over time ($\chi^2 = 2.942$, $p = 0.401$).

Table 2
Course of core NS from baseline to follow-up.

	Absence (n (%))	Onset (n (%))	Remission (n (%))	Persistence (n (%))
Any core NS	27 (30.3)	14 (15.7)	10 (11.2)	38 (42.7)[a]
N1 social anhedonia	50 (56.2)	10 (11.2)	11 (12.4)	18 (20.2)
N2 avolition	39 (43.8)	16 (18.0)	12 (13.5)	22 (24.7)
N3 expression of emotions	46 (51.7)	10 (11.2)	11 (12.4)	22 (24.7)
N4 experience of emotions and self	67 (75.3)	12 (13.5)	6 (6.7)	4 (4.5)
D4 impairment in personal hygiene	75 (84.3)	7 (7.9)	4 (4.5)	3 (3.4)

NS = negative symptoms.
[a] Participants were classified in this subgroup if they reported the presence of at least one core NS at baseline and at follow-up, irrespective of the persistence of each individual symptom (e.g. a participant reporting only item N1 as present at baseline and only item N2 as present at follow-up was classified in this group).

3.5. Core NS and transition to psychosis

At follow-up, a total of nine participants (10.1%) converted to a schizophrenia spectrum disorder (six of them had a UHR condition at baseline), 4 (4.5%) developed a UHR condition, 10 (11.2%) remitted from their UHR condition, and 6 (6.7%) met diagnostic criteria for a UHR condition at both timepoints.

A Cox regression analysis indicated that the presence of at least one core NS marginally predicted transition to psychosis at follow-up (Table 3). When core NS were examined individually, the presence of symptom N1, N4, and D4 significantly contributed to predict transition to psychosis, while N2 and N3 were below the liberal threshold of $p < 0.15$. Hence, all predictors were kept for the second step of the analyses examining the contribution of NS when combined with UHR status. In these multivariate models, only the presence of symptoms N4 and D4 remained as significant predictors (Table 3).

Cox regression analyses were also used to examine the predictive value of NS in the emergence/persistence of psychosis risk (i.e. either conversion to psychosis or presence of a UHR condition at follow-up). The presence of at least one core NS and all individual NS (except symptom N2 that was not significant but below the liberal threshold of $p < 0.15$) significantly predicted emergence/persistence of psychosis risk (Table 4). Again, all predictors were kept for the second step of the analyses examining the contribution of NS when combined with UHR status. In these multivariate models, the presence of at least one core NS, and the presence of symptoms N3, N4, and D4 remained as significant predictors (Table 4).

Age, gender, site (Geneva vs. Rome), and full-scale IQ were not significantly associated with transition to psychosis or persistence/onset of psychosis risk at follow-up when examined individually using Cox regression analyses (data not shown).

4. Discussion

Our cross-sectional and longitudinal study of NS in 22q11DS with special consideration of their contribution to psychosis risk and functional impairment revealed that "core" NS (excluding Ideational Richness and Occupational Functioning) are present in 50.5% of individuals with 22q11DS. Their severity was shown to correlate with low global functioning, and their emergence over time was associated with a specific trajectory of functional decline. Importantly, the sum score of core NS was predictive of psychosis-risk, and some individual NS contributed to significantly predict frank psychosis and/or psychosis-risk.

4.1. Prevalence, severity and course of NS in 22q11DS

At an overall rate of 73.9%, NS were the rule rather than the exception in this sample. Of the single NS, N5 (Ideational Richness) and N6

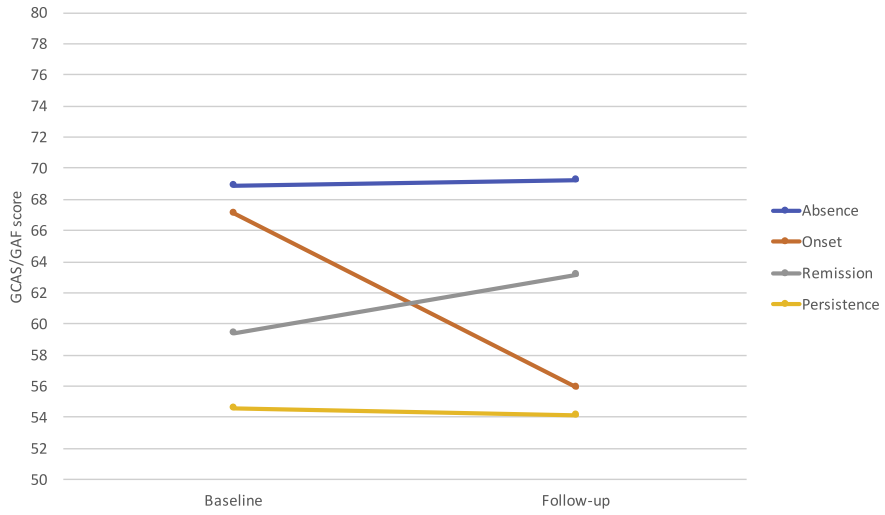

Fig. 1. Change between baseline and follow-up functioning according to the course of any core NS (absence, onset, remission, and persistence).

(Occupational Functioning) were frequently encountered and formed a distinct factor. These two items might reflect intrinsic characteristics of the 22q11DS phenotype that are related to the general cognitive profile of this population (Vorstman et al., 2015). Previous studies have shown that 22q11DS is almost always associated with difficulties in abstract reasoning, regardless of the presence of psychotic symptoms (Henry et al., 2002), and that individuals characterized by predominant negative symptoms are not characterized by more severe intellectual disability compared to those with low level of psychotic symptoms (Schneider et al., 2014b). More recently, Mekori-Domachevsky et al. (2017) observed that individuals with 22q11DS reported with higher levels of SIPS negative symptoms, including avolition and decreased expression of emotions, compared to participants with Williams Syndrome or Idiopathic Developmental Disability. Altogether, these findings and the current study suggest that NS in 22q11DS are not solely a by-product of intellectual disability and that negative symptoms and cognitive impairments are better understood as two separable dimensions. In the schizophrenia literature, there was consensus on not including cognitive difficulties and decreased functioning in the definition of NS (Kirkpatrick et al., 2006). According to several authors, decreased ideational richness (i.e. the ability to engage in abstract thinking), is commonly regarded as a disorganization symptom or positive formal thought disorder rather than a NS; and difficulties in occupational functioning are rather a consequence of avolition in terms of a NS than an NS itself (Marder and Galderisi, 2017). Furthermore, cognitive deficits and NS have also been conceptualized as representing two separable but not independent domains of the illness (Harvey et al., 2006). For these reasons, we advocate that the N5 and N6 should also not be used as a measure of NS in 22q11DS.

The remaining five NS of the SIPS that loaded on one factor likely give a more valid measure of "core" NS and were the focus of our study. 50.6% of the sample experienced at least one moderate to extreme core NS. This result is in line with the largest cross-sectional study on attenuated positive and negative symptoms in 22q11DS, which reported similar prevalence rates ranging between 7.5% for N4 and 31.0% for N2 (Weisman et al., 2017). In our study, the prevalence of core NS increased to 66.7% in the subgroup of participants meeting UHR criteria. This prevalence is slightly lower than, though likely comparable, to the 82.0% prevalence of NS reported in other clinical UHR samples (Piskulic et al., 2012), which had included N5 (17%) and the most frequent N6 (62%).

As regards the severity of NS, participants meeting UHR criteria commonly reported greater severity of NS than those not meeting UHR criteria. In addition to the sum score of core NS, the group effect became significant for items N1, N4 and D4, though only at a small to moderate effect size (Rosenthal's r: 0.196–0.235). Furthermore, longitudinal

Table 3
Cox regression models examining the role of NS in predicting transition to psychosis.

Predictors	β	SE	Wald (df)	*p*	Exp (β)	Lower 95%-CI	Upper 95%-CI
First step: individual contribution of NS. Variables are selected for the second step when $p < 0.15$							
At least one core NS present	2.004	1.071	3.499 (1)	0.061	7.417	0.909	60.527
N1 present	1.537	0.737	4.356 (1)	0.037	4.653	1.098	19.712
N2 present	1.106	0.732	2.281 (1)	0.131	3.022	0.720	12.693
N3 present	1.205	0.732	2.708 (1)	0.100	3.337	0.794	14.016
N4 present	2.489	1.072	5.391 (1)	0.020	12.048	1.474	98.477
D4 present	2.306	0.749	9.696 (1)	0.002	10.030	2.350	42.811
Second step: joint contribution of UHR status and NS							
UHR status	1.425	0.754	3.568 (1)	0.059	4.158	0.948	18.241
At least one core NS present	1.580	1.191	2.059 (1)	0.151	4.855	0.561	42.015
UHR status	1.498	0.767	3.812 (1)	0.051	4.474	0.994	20.131
N1 present	1.110	0.770	2.076 (1)	0.150	3.035	0.670	13.739
UHR status	1.679	0.741	5.128 (1)	0.024	5.360	1.253	22.925
N2 present	0.849	0.742	1.307 (1)	0.253	2.337	0.545	10.013
UHR status	1.804	0.745	5.866 (1)	0.015	6.072	1.411	26.136
N3 present	1.162	0.744	2.439 (1)	0.118	3.195	0.744	13.729
UHR status	1.800	0.736	5.987 (1)	0.014	6.050	1.431	25.588
N4 present	2.491	1.130	4.859 (1)	0.028	12.070	1.318	110.549
UHR status	1.597	0.759	4.431 (1)	0.035	4.937	1.116	21.832
D4 present	2.002	0.774	6.690 (1)	0.010	7.405	1.624	33.763

Table 4
Cox regression models examining the role of NS in predicting persistence/onset of psychosis risk (psychosis or UHR status at follow-up).

Predictors	β	SE	Wald (df)	*p*	Exp (β)	Lower 95%-CI	Upper 95%-CI
First step: individual contribution of NS. Variables are selected for the second step when $p < 0.15$							
At least one core NS present	2.115	0.751	7.930 (1)	0.005	8.290	1.902	36.133
N1 present	1.197	0.478	6.277 (1)	0.012	3.309	1.298	8.439
N2 present	0.768	0.476	2.599 (1)	0.107	2.155	0.847	5.479
N3 present	1.151	0.485	5.624 (1)	0.018	3.160	1.221	8.179
N4 present	2.117	0.689	9.433 (1)	0.002	8.310	2.152	32.094
D4 present	1.770	0.534	10.998 (1)	0.001	5.873	2.063	16.722
Second step: joint contribution of UHR status and NS							
UHR status	1.269	0.497	6.516 (1)	0.011	3.559	1.343	9.433
At least one core NS present	1.753	0.768	5.206 (1)	0.023	5.771	1.280	26.013
UHR status	1.452	0.508	8.173 (1)	0.004	4.270	1.578	11.550
N1 present	0.794	0.499	2.526 (1)	0.112	2.211	0.831	5.883
UHR status	1.593	0.492	10.478 (1)	0.001	4.918	1.875	12.902
N2 present	0.532	0.483	1.213 (1)	0.271	1.702	0.661	4.386
UHR status	1.664	0.489	11.578 (1)	0.001	5.280	2.025	13.768
N3 present	1.145	0.497	5.316 (1)	0.021	3.144	1.187	8.324
UHR status	1.660	0.488	11.591 (1)	0.001	5.258	2.022	13.671
N4 present	2.108	0.717	8.642 (1)	0.003	8.234	2.019	33.579
UHR status	1.549	0.493	9.873 (1)	0.002	4.706	1.791	12.366
D4 present	1.526	0.550	7.713 (1)	0.005	4.601	1.567	13.512

analyses revealed that, in line with reports in other clinical samples (Lyne et al., 2018), core NS predominately remained stable over time (i.e. persistently absent or present at baseline and follow-up in 73% of cases). Interesting, these numbers are in line with the trajectory of positive symptoms (see also Schneider et al., 2013; Tang et al., 2017), which might indicate a stronger co-variance of positive and negative symptoms in 22q11DS than in other clinical populations (in the present study, the course of positive and negative symptoms between baseline and follow-up was similar in almost 40% of the sample). In patients with psychosis, at least in the longer term, negative and positive symptoms likely have an independent longitudinal course, with negative symptoms displaying greater stability over time (Lyne et al., 2018). Future studies should explore in greater details the developmental course of psychotic symptoms over time in 22q11DS.

We observed that age was significantly associated with the sum of core NS as well as N3. This finding suggests that NS exacerbation occurs frequently during the early adolescence period, when individuals need to adjust to an increasingly complex environment through maturing higher order social cognitive skills (Debbane et al., 2016; Dworkin et al., 1991).

4.2. Association of NS with functioning

We observed that the severity of overall core NS as well as all five single core NS were strongly associated with global functioning. Lower baseline global functioning was associated with the presence of core NS at the same timepoint, irrespective of the evolution of these symptoms (i.e., no significant difference in baseline functioning between the absence and emergence groups, and between the remission and persistence groups). However, the group of participants experiencing an onset of core NS between baseline and follow-up was characterized by functional decline over time (on average - 11 points). In contrast, global functioning remained more stable in the other three groups. In particular, individuals who no longer experienced core NS at follow-up (remission group) showed no sign of functional recovery at follow-up. Interestingly, the functional decline observed in participants with an onset of NS appeared to be specifically driven by NS, because individuals showing an emergence of the UHR status at follow-up were not characterized by the same decline. This finding is commensurate with previous studies conducted on UHR and first-episode psychosis patients showing an association between the severity of baseline NS and poor long-term functional outcome (Meyer et al., 2014; Rabinowitz et al., 2012). Thus, NS require early targeted interventions to avoid long-term functional decline and impairment, irrespective of their role in predicting transition to psychosis.

4.3. Core NS as predictors of psychosis and of emergence/persistence of psychosis risk

Our results showed that core NS in general were not predictive of psychosis. Rather they highlighted the significant role of core NS that were experienced by only a small percentage of individuals at baseline (i.e., N4 "Experience of Emotions and Self" and D4 "Personal Hygiene") in predicting frank psychosis and/or psychosis-risk. A large body of evidence coming from research on UHR individuals has already highlighted the value of using NS as an additional indicator to predict conversion to psychosis (Clark et al., 2016; Demjaha et al., 2012; Nelson et al., 2013; Piskulic et al., 2012; Schlosser et al., 2012), as well as onset of (attenuated) positive psychotic symptoms (Tang et al., 2017). However, the precise role of single NS and their potential interplay with various group characteristics remains to be further understood, as reports of studies on UHR samples are still conflicting (Chen et al., 2016; Riecher-Rössler et al., 2009). In line with the original proposal of Cornblatt et al. (2003; Lencz et al., 2004), the inclusion of relevant core NS – likely N4 and D4 – in the definition of a clinical high risk condition should be considered for 22q11DS populations.

4.4. Strengths and limitations

While the comparable large sample size and the large follow-up rate are certainly strengths of this unique, comprehensive study, a limitation is that the trajectory of NS and functioning is inferred on the basis of two time points only, which potentially overshadows more complex patterns of development. This issue could be addressed through studies using an intensive longitudinal design. Furthermore, CGAS and GAF also consider psychopathology and thus have been criticized for nor conveying a pure measure of functioning. Thus, future studies should use "purer" and, ideally, distinct measures of role and social functioning (Cornblatt et al., 2007). Finally, participants without any longitudinal follow-up available were more severely affected from a cognitive and psychiatric point of view, despite being younger. This bias may have influenced the findings of the longitudinal analyses.

4.5. Conclusions

Core NS are present in approximately half of non-psychotic individuals with 22q11DS and are strongly related to global functioning,

irrespective of their role in predicting transition to psychosis or psychosis-risk. Therefore, the presence of NS should be a primary target of early therapeutic intervention in this population in order to improve both short- and long-term functional outcome. In addition, our study indicates that impairments in both Experience of Emotion and Self, and Personal Hygiene are specifically relevant to increase the ability to predict the emergence/persistence of psychosis risk and the transition to psychosis compared to UHR criteria alone in 22q11DS. These findings provide important new information that might help refining predictive criteria for transition to psychosis in this population.

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Contributors

Maude Schneider, Marco Armando, and Stephan Eliez designed the study and wrote the protocol. Maude Schneider and Marco Armando did the literature searches, undertook the statistical analyses, and wrote the first draft of the manuscript. Frauke Schultze-Lutter provided statistical inputs. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

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