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Predominant negative symptoms in 22q11.2 deletion syndrome and their associations with cognitive functioning and functional outcome

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Abstract

22q11.2 deletion syndrome (22q11.2DS) is a neurogenetic condition associated with increased risk for schizophrenia. No study do date has explored how positive and negative symptoms of psychosis are distributed among individual patients with 22q11.2DS and if distinct patterns of symptoms can be identified. Negative symptoms being more frequent than positive symptoms in 22q11.2DS, we expected that a high number of patients would display predominant negative symptoms (PNS), whereas predominant positive symptoms would be less frequently experienced. The present study aims at investigating the cognitive deficits and functional outcome associated with distinct patterns of psychotic symptoms in 22q11.2DS. 63 adolescents and young adults with 22q11.2DS participated in this study. Each participant underwent a clinical and a cognitive evaluation. A cluster analysis was used to identify groups of individuals with distinct patterns of symptoms. Individuals from the different clusters were then compared on a series of cognitive measures and on functional outcome. Three clusters of individuals were identified: low levels of symptoms, PNS, and high levels of symptoms. Individuals with PNS had significantly lower visual memory scores and decreased processing speed compared to participants with low levels of symptoms. They were also rated as having lower functional and occupational outcome. The present results indicate that one third of adolescents and young adults with 22q11.2DS display PNS. This pattern of symptoms was associated with specific cognitive deficits and decreased functional outcome. Future studies are needed to examine the developmental trajectories of these individuals and assess their risk of conversion to full-blown psychosis.

Keywords: 22q11.2 deletion syndrome; negative symptoms; psychotic symptoms; cluster

1. Introduction

22q11.2 deletion syndrome (22q11.2DS) is a neurogenetic condition affecting 1/4300-7000 live births (Oskarsdóttir et al., 2004) and associated with a markedly elevated risk for schizophrenia spectrum disorders (Murphy, 2005). Transient positive psychotic manifestations are experienced by more than 50% of adolescents and 20% of children with this syndrome (Baker & Skuse, 2005; Debbané et al., 2006; Schneider et al., in press). Attenuated negative symptoms are also an integral part of the 22q11.2DS profile, as they are present in up to 80% of adolescents (Schneider et al., 2012; Stoddard et al., 2010). A previous study by our group established that negative symptoms in 22q11.2DS are divided in two main dimensions relating to decreased emotional expressiveness (expressive symptoms) and social withdrawal/amotivation (amotivation symptoms) (Schneider et al., 2012). While single dimensions of early psychotic manifestations have been well described in this syndrome, the actual relationship between positive (hallucination and delusion-like symptoms) and negative symptoms (expressive and amotivation symptoms) has yet to be explored. The use of cluster analysis is a well-suited way to examine if distinct patterns of positive and negative symptoms are identifiable among 22q11.2DS individuals. Cluster analyses on psychotic-like symptoms in individuals without 22q11.2DS usually delineate four patterns of symptoms: low levels of symptoms, predominant positive symptoms (PPS), predominant negative symptoms (PNS), and high levels of symptoms (e.g. Barrantes-Vidal et al., 2010). These results indicate that positive and negative symptoms are not always concurrent, which argues in favour of distinct etiological factors leading to the expression of these two symptomatic dimensions.

The identification of a group of 22q11.2DS individuals scoring high on a single dimension of psychotic symptoms (i.e. individuals with PPS or PNS) would help disentangle the specific contribution of several factors in the pathogenesis of positive and negative symptoms. In

particular, we seek to identify if specific cognitive deficits are associated to the presence of predominant positive and negative symptoms in 22q11.2DS. Research in the field of schizophrenia indicates that negative symptoms are strongly associated to cognitive impairments, even if the precise nature of their relationship is still not fully established (Harvey et al., 2006). More specifically, negative symptoms have been associated with various cognitive domains, such as processing speed (Lipkovich et al., 2009; McDowd et al., 2011), working memory (Kebir & Tabbane, 2008; O'Gráda et al., 2009; Szendi et al., 2006), long-term memory (McDowd et al., 2011), executive functioning (Clark et al., 2010; Lewandowski et al., 2011), and attention (Sanz et al., 2012; Tsai et al., 2010). On the opposite, positive symptoms are thought to be largely independent of cognitive functioning (e.g. Green & Nuechterlein, 1999).

In a second part of the study, we also aimed at investigating the impact of predominant positive and negative symptoms on educational and professional outcome. Indeed, previous studies have suggested that some 22q11.2DS individuals have a poorer outcome than what would have been expected based on their cognitive level (Butcher et al., 2012). In our opinion, the presence of negative symptoms may be a contributing factor for poor vocational outcome in 22q11.2DS, as it has been observed in patients with schizophrenia (for a review, see Mäkinen et al., 2008). On the opposite, positive symptoms have been related to outcome to a much lesser extent (e.g. Rabinowitz et al., 2012).

The present study examines the cognitive and functional characteristics associated with individual dimensions of psychotic symptoms in adolescents and young adults with 22q11.2DS. Specifically, we formulated three main hypotheses. First, we expected that individuals would cluster in four groups according to their pattern of positive and negative symptoms: low levels of symptoms, PPS, PNS, and high levels of symptoms. Given the high prevalence of negative symptoms in 22q11.2DS (Schneider et al., 2012; Stoddard et al., 2010), we expected that a

substantial proportion of individuals would be characterized by PNS, whereas only a small group would display PPS. Secondly, we examined which cognitive dimensions were associated with the presence of predominant positive and negative symptoms and expected to observe strong associations between PNS and cognitive deficits. Finally, we explored if participants with PPS or PNS were characterized by decreased functional and vocational outcome. Again individuals with PNS were expected to have particularly low outcome. Finally, due to the strong associations between anxiety and outcome in individuals with 22q11.2DS (Angkustsiri et al., 2012), we examined the contribution of internalizing symptoms (anxiety/depression) to the observed findings.

2. Material and Methods

2.1. Participants

63 participants with 22q11.2DS aged between 10 and 28 years were included in the study (m = 16.96, sd = 4.17, 33 (52.4%) females). The presence of a 22q11.2 microdeletion was confirmed using using quantitative fluorescent polymerase chain reaction (QF-PCR). 21 (33.3%) participants were receiving psychotropic medication at the time of testing: 10 (15.9%) were on methylphenidate, 6 (9.5%) on antidepressants, 6 (9.5%) on antipsychotics, and 3 (4.8%) on anticonvulsants.

22q11.2DS participants were recruited through advertisements in patient association newsletters and through word of mouth. Written informed consent was obtained from participants and their parents under protocols approved by the Institutional Review Board of the Department of Psychiatry at the University of Geneva Medical School.

2.2. Materials

2.2.1. Clinical Assessment

The presence of psychiatric disorders was evaluated in adolescents below 18 years using the Diagnostic Interview for Children and Adolescent – Revised (DICA-R; Reich, 2000) and the psychosis supplement from the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997). Adult participants were screened using the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I; First et al., 1996).

The presence of attenuated positive and negative symptoms of schizophrenia was assessed using two evaluation scales. The Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003) evaluates positive, negative, disorganization and general prodromal symptoms. Symptoms are assessed on a 7-point severity scale (ranging from 0 to 6). For more direct comparison with the results obtained with the PANSS, we rescored the SIPS items on a scale ranging from 1 to 7. The Positive And Negative Symptom Scale (PANSS; Kay et al., 1967) is composed of a positive, negative and general psychopathology subscale. All symptoms are rated on a 7-point severity scale (ranging from 1 to 7).

In a previous study published by our group (Schneider et al., 2012), a factor analysis using the PANSS and the SIPS items enabled to identify one positive and two negative dimensions (i.e. expressive and amotivation dimensions). In the present study, we used the same dimensions and computed three symptom scores as followed: positive score (mean of SIPS P1, P2, P3, P4, D2 and PANSS P1, P2, P3, P4, P5, P6, P7), expressive score (mean of SIPS N3, N4 and PANSS N1, N2, N6, N7, G7), and amotivation score (mean of SIPS N1, N2, D4 and PANSS N4, G16). In the original factor analysis, PANSS item N5 (difficulty in abstract thinking) loaded on the expressive

dimension of negative symptoms. However in the present paper, we decided to remove this item in order to avoid redundancy with the cognitive scores, which could inflate correlations.

Finally, the parents of all participants completed the Child Behaviour CheckList (CBCL; Achenbach & Rescorla, 2001) or the Adult Behaviour CheckList (ABCL; Achenbach & Rescorla, 2003) to obtain a global parental report of behavioural difficulties. Specifically, we used the anxious-depressed t-score as a measure of anxiety/depression.

2.2.2. Cognitive assessment

Each participant underwent a general cognitive evaluation using the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991) or the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) in the context of the clinical assessment. Using additional evaluation tools, six neurocognitive skills were also examined: processing speed, verbal memory, visual memory, working memory, attention, and executive functioning.

Processing speed was assessed using the Processing Speed Index from the WISC-III or WAIS-III.

The three memory domains were assessed using subtests from the Children Memory Scale (CMS; Cohen, 1997) or the Wechsler Memory Scale (WMS-III; Wechsler, 1987). Verbal memory was assessed using the Verbal Paired Associates Immediate standard score, visual memory was assessed using the Face Memory Immediate standard score, and working memory was assessed using the Digit Span Backward standard score.

Attention was assessed using the Conners' Continuous Performance Test – II (CPT-II; Conners, 2000). Specifically, we used the attentiveness score (d') t-score provided by the computer program. We were not able to obtain the CPT scores for two participants because of a technical problem so we replaced their attentiveness score by the sample mean score (53.96).

Finally, executive functioning was assessed using the number of total correct answers during the Semantic Verbal Fluency Test (animal naming).

2.2.3. Functional outcome

During the clinical evaluation, the Global Assessment of Functioning (GAF) was completed to assess the overall level of functioning on a scale ranging from 0 to 100.

The participants' level of education or professional status was systematically recorded and used to determine educational/professional outcome. Based on this information, the participants' educational or professional outcome was classified into 8 categories (ordinary school, vocational training, gainful employment, special school, specialized vocational training, sheltered employment, no activity, and other). These categories were then merged into two main domains: ordinary (ordinary school, vocational training, and gainful employment) and special needs (special school, specialized vocational training, sheltered employment, no activity and other)

Finally, parents of 51 individuals (70% of the entire sample) were interviewed using the Vineland Adaptive Behaviour Scales (VABS; Sparrow et al., 1984) to obtain information about adaptive functioning in various domains: communication, daily-life functioning, and socialization. At the time of data collection, VABS interview were not systematically conducted for individuals older than 18 years. This is the reason why 12 individuals aged 19 years or higher have no VABS interview.

2.3. Statistical analyses

We first used a cluster analysis approach to test our first hypothesis regarding the presence of four clusters of individuals with different symptom profiles. Specifically, we used the positive, expressive and amotivation scores as classification variables and followed the procedure

suggested by Milligan (1980, quoted by Clatworthy et al., 2005). We first performed a hierarchical cluster analysis to determine the appropriate number of clusters. Then, we performed a K-means cluster analysis to optimize the results. Finally, the mean severity of symptoms was compared across the different clusters using multiple ANOVAs with post-hoc Tukey HSD comparisons.

Cognitive functioning and functional outcome (GAF score) were compared across the different clusters using ANOVAs. In order to characterize the associations between cognitive functioning, functional outcome, and individual symptomatic dimensions (positive, expressive, and amotivation symptoms), Pearson correlations were performed.

The participants' educational or professional status was also compared between the groups using Chi-Square tests.

All the analyses were performed using SPSS version 19.

3. Results

3.1. Cluster analysis

In the total sample, positive, amotivation and expressive symptom dimensions were correlated with one another ($r_{positive\text{-}amotivation}$ = 0.619, p<0.001; $r_{positive\text{-}expressive}$ = 0.694, p<0.001; $r_{amotivation\text{-}expressive}$ = 0.804, p<0.001). This indicates that, on average, these symptoms tend to occur together. Nevertheless, some degree of variability in the participants' symptom profile can be observed on the scatter plots (see Figure 1), which may be suggestive of distinct clusters of individuals.

The hierarchical cluster analysis using the positive, amotivation and expressive symptom scores as classification variables and the dendrogram indicated a three-cluster solution. We then performed a k-means cluster analysis and forced a three-cluster solution. The selection of the

three-cluster solution was supported by the high agreement between the two classification methods (kappa = 0.745, $p<0.001$). In addition, when the three symptom scores were entered into a discriminant function analysis, the three clusters were largely distinct in discriminant function space (see Figure 2).

The 63 participants were divided into the three clusters as followed: 35 participants were included in cluster 1, 21 participants in cluster 2, and 7 participants in cluster 3. The mean severity of the positive, amotivation, and expressive symptoms significantly differed between the three groups (see Figure 3): individuals from clusters 1 and 2 differed regarding the severity of amotivation and expressive symptoms ($p<0.001$) but not positive symptoms ($p=0.176$). Individuals from cluster 3 differed from the other groups on all symptomatic dimensions (all $p<0.001$). Clusters were labeled based on the patterns of positive and negative symptoms: low levels of symptoms (cluster 1); predominant negative symptoms (PNS) (cluster 2); high levels of symptoms (cluster 3). The clinical characteristics of participants in the three groups are provided in Table 1.

In accordance with our first hypothesis, a substantial group of participants was characterized by PNS. Comparing individuals included in cluster 2 (PNS) from individuals included in cluster 1 (low levels of symptoms) enables to examine the relationship between negative symptoms, cognitive functioning and functional outcome, by excluding the influence of positive symptoms. However and contrary to our hypothesis, no cluster brought together individuals with predominant positive symptoms (PPS). This prevented from examining the relationship between positive symptoms, cognitive functioning, and outcome, by excluding the influence of negative symptoms. Individuals included in cluster 3 (high levels of symptoms) were not compared with other participants' groups, as they displayed comorbid positive and negative symptoms.

3.2. Characterization of individuals with PNS

3.2.1. Cognitive functioning

One participant from cluster 2 was diagnosed with a psychotic disorder. All the analyses were performed with and without inclusion of this participant to examine his influence on the results.

Participants with low levels of symptoms and individuals with PNS did not significantly differ regarding age (t = -1.308, p=0.197), gender distribution (χ^2 = 0.172, p=0.678), or full-scale IQ (t = 0.643, p=0.523) (see Table 2).

We performed a multiple ANOVA with the six cognitive scores as independent variables (see Table 2). Participants with PNS had significantly lower scores than individuals with low levels of symptoms on the Face Memory Immediate subtest (F(1,54) = 5.412, p=0.024). The group difference for the Processing Speed Index approached significance (F(1,54) = 3.954, p=0.052). When the participant diagnosed with a psychotic disorder was excluded from the analyses, participants with PNS had significantly lower scores on the Face Memory Immediate subtest (F(1,53) = 5.138, p=0.028) and the Processing Speed Index (F(1,53) = 4.782, p=0.033).

In individuals with PNS, the Processing Speed Index was significantly correlated with the severity of expressive symptoms (r = -0.496, p=0.022), but not amotivation symptoms (r = -0.271, p=0.235). Correlations with individual SIPS or PANSS items revealed that the Processing Speed Index was significantly correlated with PANSS items N1 (blunted affect; r = -0.464, p=0.034), N6 (lack of spontaneity; r = -0.459, p=0.036), and N7 (stereotyped thinking; r = -0.646, p=0.002). The Face Memory Immediate subtest was not significantly associated with the two dimensions of negative symptoms (both p>0.05). Of note, full-scale IQ was not significantly associated with expressive or amotivation symptoms in individuals with PNS (both p>0.05).

3.2.2. Outcome

There was a highly significant difference in the mean GAF score between the two groups (t = 4.258, $p<0.001$), individuals with PNS having significantly lower GAF scores (see Table 2).

The participants' educational or professional outcome is displayed in Table 3. The comparison between the ordinary and the special needs categories revealed a significant difference between the two groups ($\chi^2 = 5.531$, $p=0.019$). Specifically, a greater proportion of participants with PNS had special needs regarding education or employment compared to participants with low levels of symptoms.

Finally, we compared the two groups regarding their level of adaptive functioning in various domains. VABS interviews were available for 30 individuals with low levels of symptoms (86%) and 16 individuals with PNS (76%). A multiple ANOVA revealed a significant group difference for the socialization domain ($F(1,44) = 5.112$, $p=0.029$). The communication and daily-life functioning domains were not significantly different between the two groups (both $p>0.05$).

The group comparisons remained unchanged when the participant diagnosed with a psychotic disorder was excluded from the analyses.

In individuals with PNS, the GAF score was significantly correlated with the severity of amotivation symptoms ($r = -0.562$, $p=0.008$) but not expressive symptoms ($r = -0.296$, $p=0.193$). Correlations with individual SIPS or PANSS items revealed that the GAF score was significantly correlated with SIPS item D4 (decreased personal hygiene; $r = -0.503$, $p=0.020$), and PANSS item N7 (stereotyped thinking; $r = -0.487$, $p=0.025$). The VABS domains were not significantly correlated with the severity of amotivation or expressive symptoms (all $p>0.05$).

The results remained unchanged when the level of anxiety/depression (CBCL anxious-depressed t-score) was taken into account.

4. Discussion

A large body of research has contributed to the understanding of attenuated psychotic symptoms in 22q11.2DS (e.g. Armando et al., 2012; Debbané et al., 2006; Gothelf et al., 2007). However, no study to date has investigated how attenuated positive and negative symptoms are distributed among 22q11.2DS adolescents and young adults. The present study is a first attempt to identify homogeneous subgroups of patients based on their symptomatology. Contrary to our hypothesis, the cluster analysis established the presence of only three clusters: low levels of symptoms, high levels of symptoms, and predominant negative symptoms (PNS).

Cluster analyses in participants without 22q11.2DS usually delineate a fourth cluster, which includes individuals with predominant positive symptoms (Barrantes-Vidal et al., 2010). This difference suggests that the severity of negative symptoms represent the predominant clinical characteristic of psychotic expression in 22q11.2DS. Indeed, negative symptoms seem to be present in the majority of adolescents and young adults and to appear either alone or together with positive symptoms. Furthermore, our results indicate that PNS are frequent, as approximately one third of the participants were included in this subgroup. This is consistent with previous studies showing that negative symptoms are more frequent and severe than positive symptoms in this population (Schneider et al., 2012; Stoddard et al., 2010). Furthermore, Armando et al. (2012) observed that individuals at ultra-high risk for schizophrenia with and without 22q11.2DS differed regarding the severity of negative symptoms but not positive or disorganization symptoms.

The frequency of negative symptoms in 22q11.2DS raises the important issue of the differential diagnosis of negative symptoms in this population, and more broadly in individuals with

developmental disabilities. First, differential diagnosis between negative symptoms and autistic traits should be considered, as both are characterized by marked impairments in the social area. Nevertheless, the developmental trajectory of social impairments in the context of negative symptoms/increased risk for schizophrenia or autism spectrum disorder (ASD) is different: whereas individuals with ASD experience early impairments in the social area, those who develop schizophrenia typically experience a decrease in social competences and functioning from the beginning of adolescence (see Salokangas & McGlashan, 2008). To our knowledge, no study to date has investigated the developmental trajectory of social impairments from early childhood until adolescence in 22q11.2DS. This should be performed in future studies in order to better delineate the social phenotype in 22q11.2DS. Secondly, negative symptoms in 22q11.2DS are often viewed as a direct consequence of lower intellectual functioning and therefore as being unrelated to schizophrenia. However, we observed that individuals with PNS did not differ from individuals with low levels of symptoms regarding general intellectual functioning. This argues against the causal role of intellectual disability in the presence of negative symptoms. Finally, negative symptoms can appear as a side effect of psychotropic medication. Again, this doesn't seem to be the case in the present sample, as only 19% of individuals with PNS were receiving psychotropic medication at the time of testing. In comparison, this percentage was higher (37%) in the group of patients with low levels of symptoms.

Despite the clinical significance of negative symptoms in 22q11.2DS, very few studies have focused on these manifestations and no study to date explored the cognitive factors that may contribute to their emergence. The present study suggests that individuals with PNS have specific cognitive impairments compared to individuals with low levels of symptoms. Specifically, this subgroup of patients had a significant decrease in visual memory, whereas verbal memory was not impaired. An important difference between the tasks assessing visual and verbal memory is

the use of social vs. non-social material. Visual memory was assessed using a face memory task, and verbal memory using a paired associates task. It may be the case that a deficit in memory of social information contributes to the presence of negative symptoms in 22q11.2DS. Indeed, it has been shown that abnormal visual exploration strategies contribute to face processing difficulties in 22q11.2DS (Campbell et al., 2010; Glaser et al., 2010). It is possible that abnormal visual exploration during social interactions contributes to memory deficits for social information and to disturbed relationships to the environment, which manifest themselves by an increase in negative symptoms. Further studies investigating several aspects of social cognition in 22q11.2DS are needed to confirm and extend this hypothesis. If future work supports the role of social cognitive deficits in the pathogenesis of negative symptoms, children and adolescents with 22q11.2DS should benefit from socio-cognitive remediation programs (see Glaser et al., 2012).

Processing speed was also decreased in participants with PNS and was mainly associated with the expressive dimension of negative symptoms. These results suggest that processing speed contributes to the clinical expression of negative symptoms and may act as a non-specific factor of resource limitation (see Rector, 2005). Indeed, decreased processing speed may alter the ability to process ongoing information (e.g. during social interactions), which leads to a sense of failure, decreases the motivation to initiate social contacts and contributes to the development of negative symptoms.

The second aim of this study was to investigate the impact of PNS on outcome. In accordance with a previous research by our group (Schneider et al., 2012), our results indicate that individuals with PNS have significantly decreased functional and occupational outcome compared to individuals with low levels of symptoms. Specifically, our data point towards particular impairments in the area of socialization, whereas other domains were unimpaired. The difference in occupational outcome was also striking between the two groups: whereas special

needs regarding education or work were required by approximately one third of participants with low levels of symptoms, this percentage rose to almost 60% in individuals with PNS. One could argue that the observed associations between PNS and outcome were driven by other confounding factors, and especially by a difference in cognitive efficiency or internalizing symptoms (anxiety/depression) level between the two groups. However, they did not significantly differ in several potentially confounding factors such as age, gender, and full-scale IQ. Furthermore, when the analyses were controlled for the level of anxiety/depression, results remained identical. Therefore, we have good evidence to state that the presence of negative symptoms is a key contributor to this difference.

The relationship between negative symptoms and outcome stresses the importance of promoting intervention strategies in 22q11.2DS that target negative symptoms. This may improve outcome and reduce the direct and indirect costs generated by negative symptoms (e.g. loss of autonomy, employment). In particular, psychotherapeutic interventions should focus on amotivation symptoms, as they appeared to be the best predictor of outcome in the present study. There is some evidence suggesting that cognitive behavioral therapy focused on negative symptoms is effective in schizophrenic patients without 22q11.2DS (Klingberg et al., 2011; Perivoliotis & Cather, 2009). Interestingly, a recently published article showed that this type of intervention improved motivation in low-functioning patients with schizophrenia (Grant et al., 2012). This may indicate that similar strategies could be implemented in patients with 22q11.2DS to improve negative symptoms.

The results of this study should be interpreted in the light of the following limitations. First, the use of a cross-sectional design did not allow investigating the causal relationships between the studied variables. Specifically, it is still to be determined whether cognitive deficits play a causal role in the development of negative symptoms or if they appear as a consequence of them. We

are currently performing longitudinal evaluations of this cohort in order to overcome this issue. In addition, longitudinal follow-up will help to understand the developmental trajectories of individuals with PNS. In particular, the risk for the development of full-blown psychosis in this subgroup of individuals is still unknown. Longitudinal research in high-risk samples without 22q11.2DS suggests that the severity of negative symptoms has a predictive value for the development of psychosis later in life (Demjaha et al., 2012; Johnstone et al., 2005; Velthorst et al., 2009). Therefore, it is important to identify if 22q11.2DS patients with PNS are at increased risk for schizophrenia spectrum disorders and warrant a heightened monitoring of their psychotic symptoms. Finally, a major limitation relates to the use of a cognitive battery performed in the context of a clinical evaluation. This may partly explain why several cognitive domains were not specifically altered in patients with PNS. Indeed, recent conceptualizations of specific negative symptoms have supported the role of precise cognitive mechanisms that were not assessed with the present evaluation battery. For example, research has highlighted that deficits in situations involving multitasking is a key component of apathy and is strongly related to daily-life functioning (e.g. Esposito et al., 2010). The use of more theoretically oriented assessment tools should be implemented in future studies in order to better understand the role of specific cognitive deficits.

Despite these limitations, we believe that the present study contributes to the characterization of negative symptoms in 22q11.2DS, which are an important target in psychological interventions for this population. A better understanding of the cognitive difficulties contributing to their emergence will enable the development of specific neuropsychological rehabilitation strategies for 22q11.2DS patients with severe negative symptoms.

5. Bibliography

Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms and profiles. Burlington, VT: University of Vermont, Research center for children, youth, and families, 2001.

Achenbach TM, Rescorla LA. Manual for the ASEBA adult forms and profiles. Burlington, VT: University of Vermont, Research center for children, youth and families, 2003.

Angkustsiri K, Leckliter I, Tartaglia N, Beaton EA, Enriquez J, Simon TJ. An examination of the relationship of anxiety and intelligence to adaptive functioning in children with chromosome 2211.2 deletion syndrome. Journal of Developmental and Behavioural Pediatrics 2012; 33: 713-720.

Armando M, Girardi P, Vicari S, Menghini D, Digilio MC, Saba R, Mazzone L, Lin A, Klier CM, Schäfer MR, Amminger GP. Adolescents at ultra high risk for psychosis with and without 22q11 deletion syndrome: A comparison of prodromal psychotic symptoms and general functioning. Schizophrenia Research 2012; 139: 151-156.

Baker KD, Skuse DH. Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. The British Journal of Psychiatry 2005; 186: 115-120.

Barrantes-Vidal N, Lewandowski KE, Kwapil TR. Psychopathology, social adjustment and personality correlates of schizotypy clusters in a large nonclinical sample. Schizophrenia Research 2010; 122: 219-225.

Butcher NJ, Chow EWC, Costain G, Karas D, Ho A, Bassett AS. Functional outcomes of adults with 22q11.2 deletion syndrome. Genetics in Medicine 2012; 14: 836-843.

Campbell L, McCabe K, Leadbeater K, Schall U, Loughland C, Rich D. Visual scanning of faces in 22q11.2 deletion syndrome: Attention to the mouth or the eyes? Psychiatry Research 2010; 177: 211-215.

Clark LK, Warman D, Lysaker PH. The relationships between schizophrenia symptom dimensions and executive functioning components. Schizophrenia Research 2010; 124: 169-175.

Clatworthy J, Buick D, Hankins M, Weinman J, Horne R. The use and reporting of cluster analysis in health psychology: a review. British Journal of Health Psychology 2005; 10: 329-358.

Cohen M. Children's memory scale. London: The Psychological Corporation, 1997.

Conners C. Conners' continuous performance test (CPT-II): computer program for Windows technical guide and software manual. Toronto: MHS, 2000.

Debbané M, Glaser B, David MK, Feinstein C, Eliez S. Psychotic symptoms in children and adolescents with 22q11.2 deletion syndrome: Neuropsychological and behavioral implications. Schizophrenia Research 2006; 84: 187-193.

Demjaha A, Valmaggia L, Stahl D, Byrne M, McGuire P. Disorganization/Cognitive and Negative Symptom Dimensions in the At-Risk Mental State Predict Subsequent Transition to Psychosis. Schizophrenia Bulletin 2012; 38: 351-359.

Esposito F, Rochat L, Juillerat Van der Linden A-C, Lekeu F, Quittre A, Charnallet A, Van der Linden M. Apathy and executive dysfunction in alzheimer disease. Alzheimer disease and associated disorders 2010; 24: 131-137.

First M, Gibbon M, Spitzer R, Williams J. Structured clinical interview for the DSM-IV Axis I disorders (SCID-I): American Psychiatric Association, 1996.

Glaser B, Debbané M, Ottet M-C, Vuilleumier P, Zesiger P, Antonarakis SE, Eliez S. Eye gaze during face processing in children and adolescents with 22q11.2 deletion syndrome. Journal of the American Academy of Child and Adolescent Psychiatry 2010; 49: 665-674.

Glaser B, Lothe A, Chabloz M, Dukes D, Pasca C, Redouté J, Eliez S. A candidate socio-emotional remediation program for individuals with intellectual disability. American Journal on Intellectual and Developmental Disabilities 2012; 117: 368-383.

Gothelf D, Feinstein C, Thompson T, Gu E, Penniman L, Van Stone E, Kwon H, Eliez S, Reiss AL. Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome. The American journal of psychiatry 2007; 164: 663-669.

Grant PM, Huh GA, Perivoliotis D, Stolar NM, Beck AT. Randomized Trial to Evaluate the Efficacy of Cognitive Therapy for Low-Functioning Patients With Schizophrenia. Archives of General Psychiatry 2012; 69: 121-127.

Green MF, Nuechterlein KH. Should schizophrenia be treated as a neurocognitive disorder? Schizophrenia Bulletin 1999; 25: 309-319.

Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophrenia Bulletin 2006; 32: 250-258.

Johnstone E, Ebmeier K, Miller P, Owens D, Lawrie S. Predicting schizophrenia: findings from the Edinburgh High-Risk Study. British Journal of Psychiatry 2005; 186: 18-25.

Kaufman J, Birmaher B, Brent D, Rao U. Schedule for affective disorders and schizophrenia for school-age children-present lifetime version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry 1997; 36: 980-988.

Kay SR, Fiszbein A, Opier LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia Schizophrenia Bulletin 1967; 13: 261-276.

Kebir O, Tabbane K. [Working memory in schizophrenia: a review]. Encephale 2008; 34: 289-298.

Klingberg S, Wölwer W, Engel C, Wittorf A, Herrlich J, Meisner C, Buchkremer G, Wiedemann G. Negative symptoms of schizophrenia as primary target of cognitive behavioral therapy: results of the randomized clinical TONES study. Schizophrenia Bulletin 2011; 37 Suppl 2: S98-110.

Lewandowski K, Cohen B, Keshavan M, Ongür D. Relationship of neurocognitive deficits to diagnosis and symptoms across affective and non-affective psychoses. Schizophrenia Research 2011; 133: 212-217.

Lipkovich IA, Deberdt W, Csernansky JG, Sabbe B, Keefe RS, Kollack-Walker S. Relationships among neurocognition, symptoms and functioning in patients with schizophrenia: a path-analytic approach for associations at baseline and following 24 weeks of antipsychotic drug therapy. BMC Psychiatry 2009; 9: 44.

Mäkinen J, Miettunen J, Isohanni M, Koponen H. Negative symptoms in schizophrenia: a review. Nordic Journal of Psychiatry 2008; 62: 334-341.

McDowd J, Tang T-C, Tsai P-C, Wang S-Y, Su C-Y. The association between verbal memory, processing speed, negative symptoms and functional capacity in schizophrenia. Psychiatry Research 2011; 187: 329-334.

Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, McFarlane W, Perkins DO, Pearlson GD, Woods SW. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophrenia Bulletin 2003; 29: 703-715.

Murphy KC. Annotation: velo-cardio-facial syndrome. Journal of child psychology and psychiatry, and allied disciplines 2005; 46: 563-571.

O'Gráda C, Barry S, McGlade N, Behan C, Haq F, Hayden J, O'Donoghue T, Peel R, Morris DW, O'Callaghan E, Gill M, Corvin AP, Dinan TG, Donohoe G. Does the ability to sustain attention underlie symptom severity in schizophrenia? Schizophrenia Research 2009; 107: 319-323.

Oskarsdóttir S, Vujic M, Fasth A. Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. Archives of Disease in Childhood 2004; 89: 148-151.

Perivoliotis D, Cather C. Cognitive behavioral therapy of negative symptoms. Journal of clinical psychology 2009; 65: 815-830.

Rabinowitz J, Levine SZ, Garibaldi G, Bugarski-Kirola D, Berardo CG, Kapur S. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: Analysis of CATIE data. Schizophrenia Research 2012;

Reich W. Diagnostic Interview for children and adolescents (DICA). Journal of the American Academy of Child and Adolescent Psychiatry 2000; 39: 59-66.

Salokangas RKR, McGlashan TH. Early detection and intervention of psychosis. A review. Nordic Journal of Psychiatry 2008; 62: 92-105.

Sanz JC, Gómez V, Vargas ML, Marín JJ. Dimensions of attention impairment and negative symptoms in schizophrenia: a multidimensional approach using the conners continuous performance test in a Spanish population. Cognitive and Behavioral Neurology 2012; 25: 63-71.

Schneider M, Schaer M, Mutlu AK, Menghetti S, Glaser B, Debbané M, Eliez S. Clinical and cognitive risk factors for psychotic symptoms in 22q11.2 deletion syndrome: a transversal and longitudinal approach. European Child and Adolescent Psychiatry in press;

Schneider M, Van der Linden M, Glaser B, Rizzi E, Dahoun SP, Hinard C, Bartoloni L, Antonarakis SE, Debbané M, Eliez S. Preliminary structure and predictive value of attenuated negative symptoms in 22q11.2 deletion syndrome. Psychiatry Research 2012; 196: 277-284.

Sparrow SS, Balla DA, Cicchetti DV. Vineland Adaptive Behavior Scales. Circle Pines, MN: American Guidance Service, 1984.

Stoddard J, Niendam T, Hendren R, Carter C, Simon TJ. Attenuated positive symptoms of psychosis in adolescents with chromosome 22q11.2 deletion syndrome. Schizophrenia Research 2010; 118: 118-121.

Szendi I, Kiss M, Racsmány M, Boda K, Cimmer C, Vörös E, Kovács ZA, Szekeres G, Galsi G, Pléh C, Csernay L, Janka Z. Correlations between clinical symptoms, working memory functions and structural brain abnormalities in men with schizophrenia. Psychiatry Research 2006; 147: 47-55.

Tsai J, Lysaker PH, Vohs JL. Negative symptoms and concomitant attention deficits in schizophrenia: associations with prospective assessments of anxiety, social dysfunction, and avoidant coping. Journal of Mental Health 2010; 19: 184-192.

Velthorst E, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, Klaassen R, de Haan L, van Amelsvoort T, Linszen DH. Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophrenia Research 2009; 109: 60-65.

Wechsler D. Manual for the Wechsler memory scale - revised. San Antonio: The Psychological Corporation, 1987.

Wechsler D. Wechsler Intelligence Scale for Children - Third edition. Manual. San Antonio, TX: The Psychological Corporation, 1991.

Wechsler D. Wechsler Adult Intelligence Scale - Third edition. Administration and Scoring manual. San Antonio, TX: The Psychological Corporation, 1997.

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Figure 1: scatter plots representing the associations between positive, amotivation and expressive symptoms. For visualization's purpose, the mean of the dimensions is represented on the graphs. The positive correlations indicate that these symptoms tend to occur together. Nevertheless, some individuals display above average negative symptoms and below average positive symptoms (i.e. individuals located in the lower right quadrant of Figure 1a and 1b). A minority of individuals also seems to display above average positive symptoms and below average negative symptoms (i.e. individuals located in the upper left quadrant of Figure 1a and 1b). This suggests that different clusters of individuals can be identified.

Figure 2: participants plotted in discriminant function space

Figure 3: mean positive, amotivation and expressive scores in each cluster

Table 1: Clinical characteristics of individuals in the three clusters

	Cluster 1 Low levels of symptoms (N = 35)	**Cluster 2 Predominant negative symptoms (N = 21)**	**Cluster 3 High levels of symptoms (N = 7)**
Anxiety disorder [a]	12 (34%)	10 (48%)	3 (43%)
Mood disorder [b]	6 (17%)	2 (10%)	1 (14%)
Disruptive disorder [c]	11 (31%)	4 (19%)	1 (14%)
Psychotic disorder [d]	0 (0%)	1 (5%)	5 (71%)
Prodromal Syndrome (SIPS)	4 (11%)	5 (24%)	4 (57%)

[a] includes: simple phobia, social phobia, generalized anxiety disorder, separation anxiety disorder (only in adolescents < 18 years), obsessive-compulsive disorder, panic disorder (only in adults ≥ 18 years), and post-traumatic stress disorder
[b] includes: major depressive disorder and dysthymia
[c] includes: ADHD (only in adolescents < 18 years), oppositional defiant disorder, and conduct disorder
[d] includes: schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, and psychotic disorder NOS

Table 2: Mean (sd) for the demographics, neurocognitive and social cognitive variables in participants with low levels of symptoms (cluster 1) and predominant negative symptoms (cluster 2).

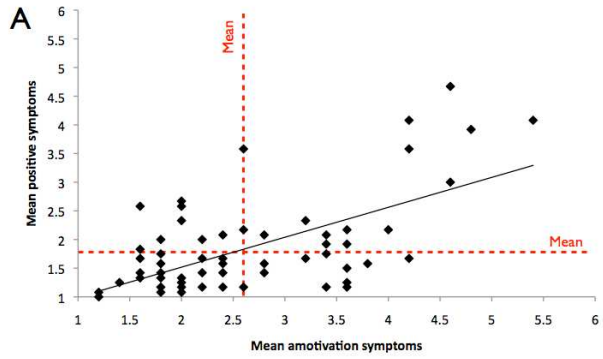
	Cluster 1 Low levels of symptoms	**Cluster 2 Predominant negative symptoms**	***P***
Age	16.24 (4.26)	17.77 (4.20)	n.s.
Gender (Females/Males - % females)	18/17 (51.4%)	12/9 (57.1%)	n.s.
Full-scale IQ	71.77 (10.53)	69.90 (10.52)	n.s.
GAF	69.40 (8.51)	58.76 (9.90)	*p < 0.001*
VABS communication	72.23 (14.67)	67.81 (16.67)	n.s.
VABS daily-life functioning	73.70 (13.56)	70.06 (14.60)	n.s.
VABS socialization	79.37 (17.64)	68.31 (11.41)	*p = 0.029*
Processing Speed Index (z-score)	0.20 (0.99)	-0.33 (0.95)	*p = 0.052*
Verbal Paired Associates Immediate SS (z-score)	-0.11 (1.01)	0.19 (0.97)	n.s.
Face Memory Immediate SS (z-score)	0.23 (1.01)	-0.39 (0.87)	*p = 0.024*
Digit Span Backward SS (z-score)	-0.05 (0.99)	0.09 (1.04)	n.s.
CPT attentiveness (d') TS (z-score)	0.06 (1.12)	-0.09 (0.77)	n.s.
Verbal Fluency total score (z-score)	0.16 (1.03)	-0.26 (0.92)	n.s.

SS = standard score
TS = t-score

Table 3: Description of the educational or professional outcome in participants with low levels of symptoms (cluster 1) and participants with predominant negative symptoms (cluster 2).

	Ordinary school	Special school	Vocational training	Specialized vocational training	Gainful employment	Sheltered employment	No activity	Other [a]	Ordinary [b]	Special needs [c]
Cluster 1: low levels of symptoms	23 (66%)	3 (9%)	2 (6%)	3 (9%)	1 (3%)	2 (6%)	1 (3%)	0 (0%)	26 (74%)	9 (26%)
Cluster 2: predominant negative symptoms	6 (29%)	5 (24%)	3 (14%)	2 (10%)	0 (0%)	3 (14%)	0 (0%)	2 (10%)	9 (43%)	12 (57%)

[a] includes homeschooling (n = 1) and voluntary work within the family enterprise (n = 1)
[b] sum of the following categories: ordinary school, vocational training, and gainful employment
[c] sum of the following categories: special school, specialized vocational training, sheltered employment, no activity, and other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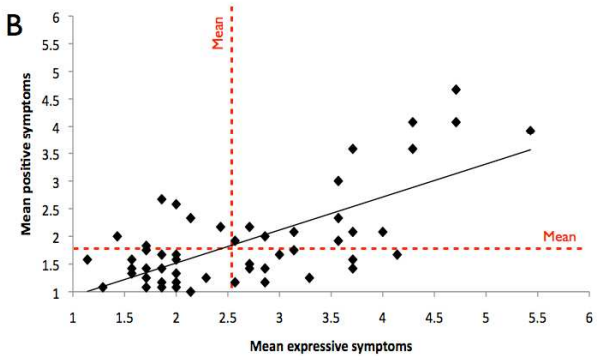
B
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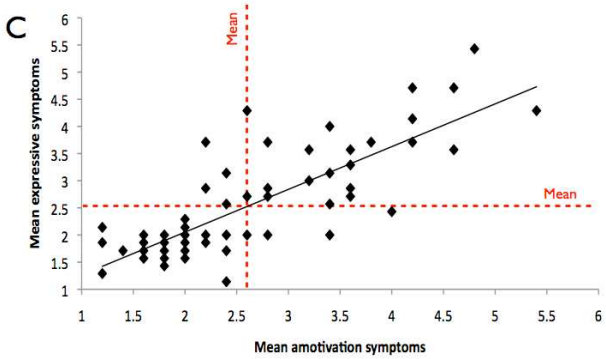
C
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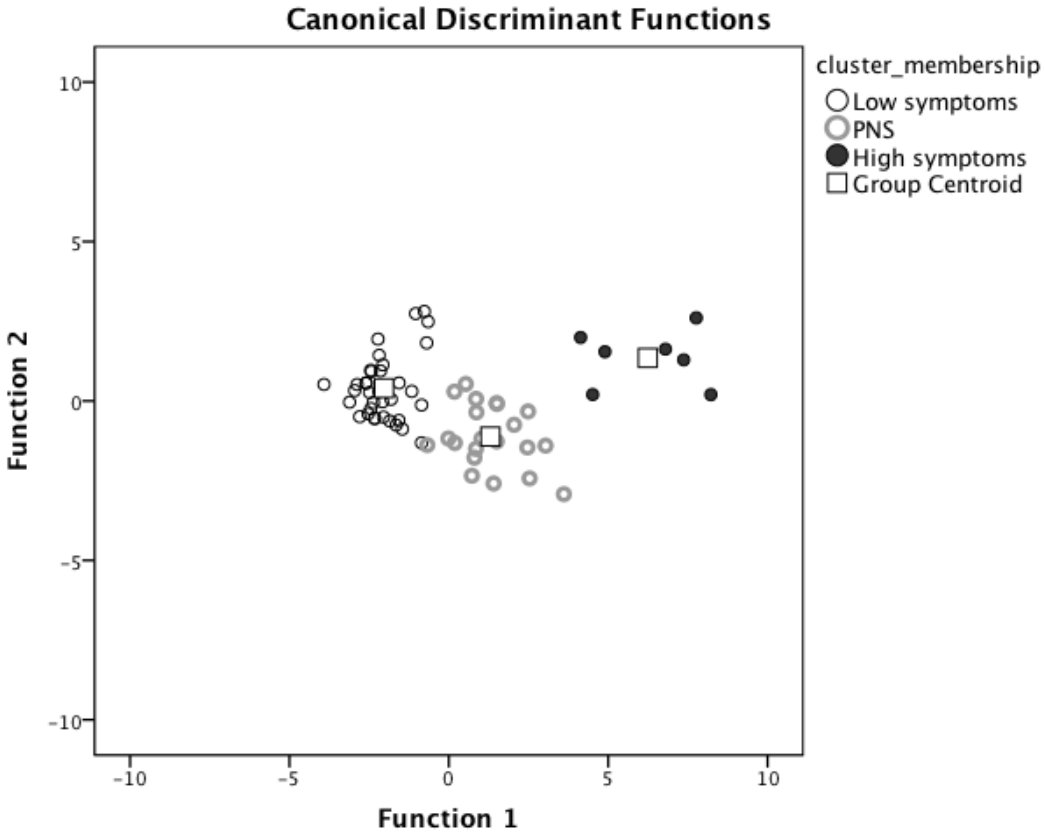

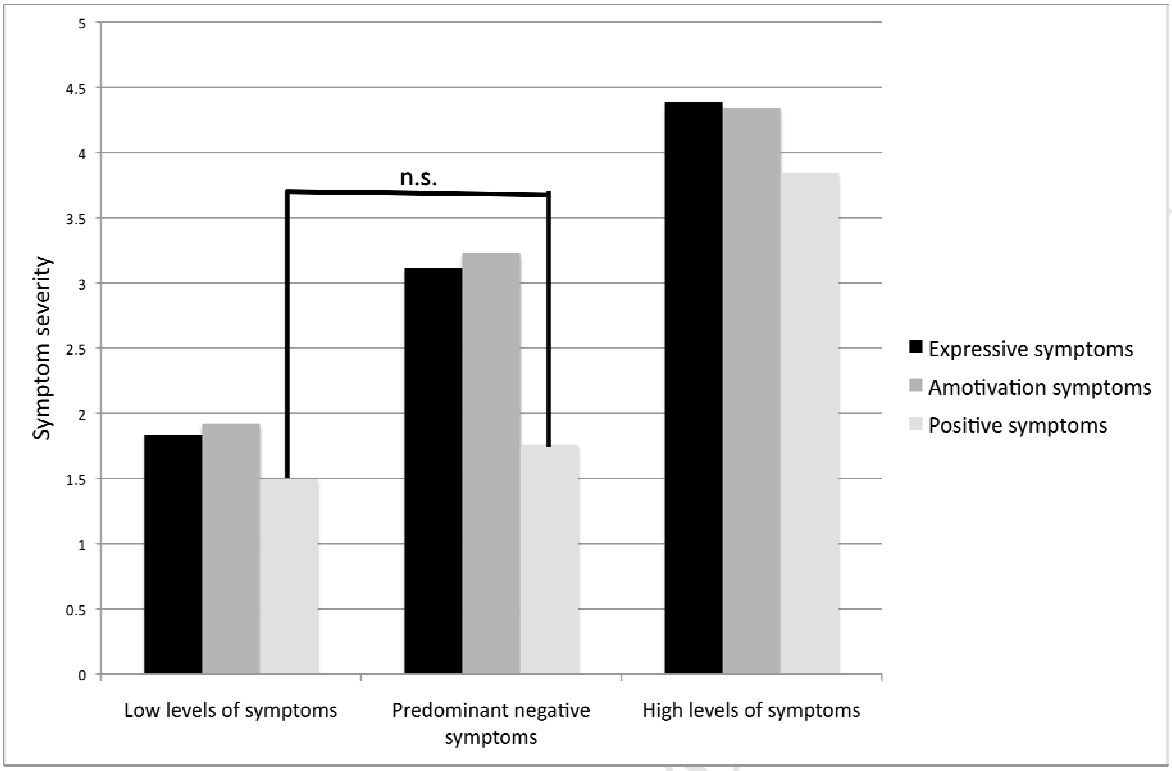

M. Schneider, M. Van der Linden, S. Menghetti, B. Glaser, M. Debbané and S. Eliez designed the study; M. Schneider, S. Menghetti, B. Glaser, M. Debbané and S. Eliez acquired the data; M. Schneider and M. Van der Linden analyzed the data and undertook the statistical analyses; M. Schneider wrote the first draft of the manuscript; all authors contributed to the interpretation of the results and the writing of the manuscript. All authors have approved the final manuscript.

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