Neurocognitive profile in psychotic versus nonpsychotic individuals with 22q11.2 deletion syndrome

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Received 23 March 2016; received in revised form 12 July 2016; accepted 1 August 2016

Abstract
The 22q11.2 deletion syndrome (22q11DS) is associated with increased rates of psychotic disorders and cognitive deficits, but large scale studies are needed to elucidate their interaction. The objective of this two-center study was to identify the neurocognitive phenotype of individuals with 22q11DS and psychotic disorders. We hypothesized that psychotic 22q11DS individuals compared to nonpsychotic deleted individuals would have more severe neurocognitive deficits, especially in executive function and social cognition. These deficits would be present when compared to IQ-matched individuals with Williams Syndrome (WS).

Three groups were ascertained from the Tel Aviv and Philadelphia centers: 22q11DS individuals with a psychotic disorder (n=31), nonpsychotic 22q11DS (n=86) and typically-developing controls (TD, n=828). In Tel Aviv a group of individuals with WS (n=18) matched in IQ to the
Neurocognition of 22q11DS with psychosis

1. Introduction

The 22q11.2 deletion syndrome (22q11DS) is one of the most common genetic syndromes, occurring in up to 1 in 1000 live births (Grati et al., 2015). It is characterized by multiple medical symptoms, including cardiac disorders, palatal abnormalities and hypocalcemia (Bassett et al., 2011; Furuya et al., 2015; McDonald-McGinn et al., 2015). Most individuals with 22q11DS cope with cognitive deficits in attention, executive function, complex cognition, social cognition and memory (Azuma et al., 2015; Gur et al., 2014b; Simon et al., 2005). In addition, psychiatric comorbidities are very common and include attention deficit/hyperactivity disorder (ADHD), depression and anxiety disorders (Schneider et al., 2014a). The syndrome is also associated with high prevalence of psychotic disorders. By adulthood about one-third of individuals with 22q11DS develop a psychotic disorder, most often schizophrenia (Gothelf et al., 2013) representing an approximately ~10-fold increase risk compared to individuals with other developmental disabilities (Hemmings, 2006).

Premorbid neurocognitive deficits in attention, verbal memory and executive function, are prominent features of schizophrenia in the general population. Some of those domains, including working memory and executive function deficits, are endophenotypes of the disorder (Tan et al., 2009).

The associations among cognitive deficits, psychosis risk and psychotic disorders have been previously studied in 22q11DS (Chow et al., 2006; Gothelf et al., 2007; van Amelsvoort et al., 2004). These studies investigated premorbid cognitive deficits as predictors for later development of psychosis (Antshel et al., 2010; Gothelf et al., 2007; Vorstman et al., 2015; Yuen et al., 2013) and focused primarily on IQ measures. They found that individuals with 22q11DS who later develop psychotic disorders or prodromal syndrome have lower baseline verbal IQ (VIQ) and more robust age associated decline in VIQ compared to 22q11DS individuals who do not develop psychotic disorders (Antshel et al., 2010; Gothelf et al., 2007; Gothelf et al., 2013; Green et al., 2009). A large sample of individuals with 22q11DS followed longitudinally, replicated these finding (Vorstman et al., 2015) and demonstrated that the decline in VIQ as early as 11 years old, was associated with later development of psychotic disorders. Such findings are consistent with reports of substantial neuropsychological decline in schizophrenia in the general population from the premorbid to the post-onset period (Meier et al., 2014).

Few studies have investigated a broad cognitive profile in individuals with 22q11DS and psychotic disorders (Chow et al., 2006; Gothelf et al., 2013; Green et al., 2009; van Amelsvoort et al., 2004). The studies that examined psychotic patients with 22q11DS did not use a single battery, and applied several tests from various cognitive batteries, including nonstandardized measures, combining computerized and noncomputerized tests (Chow et al., 2006; van Amelsvoort et al., 2004). These studies reported that individuals with psychotic disorders and 22q11DS, compared with non-psychotic 22q11DS individuals, had poorer motor skills and more deficits in verbal learning and social cognition (Chow et al., 2006). Deficits in spatial working memory, strategy formation, attention and visual recognition have also been reported in individuals with 22q11DS and psychotic disorders (van Amelsvoort et al., 2004). To better characterize the cognitive deficits in psychotic individuals with 22q11DS, it is important to employ a single computerized comprehensive neurocognitive battery and to include both healthy and developmentally delayed controls.

In addition to being the first study to use a comprehensive computerized cognitive battery for 22q11DS psychotic individuals, the current study is also the first to compare cognitive characteristics in 22q11DS psychotic individuals with an IQ matched group of individuals with another common microdeletion disorder. Williams syndrome (WS) is an optimal control group for psychotic patients with 22q11DS because the mean IQ of individuals with WS is ~60 (Mervis et al., 2000), which is similar to the reported IQ of 22q11DS individuals with psychotic disorders (Vorstman et al., 2015). Additionally, individuals with 22q11DS and WS have a high prevalence of similar physical comorbidities including cardiac deficits, feeding difficulties, and calcium abnormalities (Zarchi et al., 2014). The two groups also share high rates of psychiatric disorders and problems with peer relations (Zarchi et al., 2014).

The aim of the present two-site study was to characterize the cognitive phenotype of individuals with 22q11DS and psychotic disorders by comparing them to age-matched 22q11DS individuals without psychotic disorders, to
Table 1  Demographic characteristic of the Tel Aviv and Philadelphia cohorts.

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<td>Age (Mean)</td>
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<td>26.8 (6.6)</td>
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<td>50/50</td>
<td>66/34</td>
<td>47/53</td>
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<tr>
<td>Parent Edu</td>
<td>13.85 (2.1)</td>
<td>14.05 (2.05)</td>
<td>14.72 (2.2)</td>
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<td>FSIQ Mean</td>
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<td>66.6 (11.0)</td>
<td>78.6 (10.5)</td>
<td>103.23 (7.6)</td>
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<td>(SD)</td>
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<tr>
<td>FSIQ Mean</td>
<td>14.65 (2.32)</td>
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22q11.2 Deletion Syndrome, 22q11DS; TD, Typically developing; N, Number of participants; M, Mean; SD, Standard Deviation; Parent Edu, Average parent’s number of years in a formal educational setting; FSIQ, Full scale intelligence quotient; NA, Not Available.

P-values between 22q11DS psychotic and nonpsychotic groups for age, parent education and FSIQ are determined by ANOVA; sex was calculated using Chi-square test.
IQ-matched group with WS and to typically developing (TD) controls using the Penn Computerized Neurocognitive Battery (CNB). The CNB is a single computerized battery which rules out potential limitations of combining tests from multiple batteries. It was developed for large-scale genomic studies (Gur et al., 2012), applied in developmental samples (Satterthwaite et al., 2014), schizophrenia consortia (Calkins et al., 2010; Gur et al., 2014a; Gur et al., 2010), studies of 22q11DS (Gur et al., 2014b; Yi et al., 2015a) and is highly correlated with IQ (Swagerman et al., 2016). This is the first international study that uses the CNB for identifying the broad cognitive phenotype of 22q11DS with psychotic disorders. Based on previous studies in 22q11DS and schizophrenia in the general population, we hypothesized that psychotic patients with 22q11DS would be characterized by the following features: 1. More robust deficits across neurocognitive domains compared to TD controls; 2. Psychotic individuals with 22q11DS, compared to nonpsychotic 22q11DS, would have greater deficits in executive function and social cognition domains; 3. These deficits would be present when the subjects are compared to an IQ-matched group of subjects with WS.

2. Experimental procedures

2.1. Participants

2.1.1. Tel Aviv

The cohort was recruited from the Behavioral Neurogenetic Center at the Sheba Medical Center, Tel Aviv University. This large referral center coordinates research and treatment of individuals with 22q11DS and WS. Only individuals with a FSIQ ≥ 60 were included in the study. The diagnosis of 22q11DS and WS was confirmed using fluorescence in situ hybridization (FISH) test and multiplex ligation-dependent probe amplification (MLPA). Typically developing controls were recruited through advertisements within the local community. Only TD controls without major psychopathology were included. Psychopathology was ruled out by a structured screening of all TDs using the Scoring of Procedures Manual questionnaire (SCL90) (Derogatis, 1992).

Forty-five participants with 22q11.2DS and 33 TD were recruited. 22q11DS and TD participants were similar in mean age, parental education, mean number of school years completed by two parents and sex distribution, but the 22q11DS had significantly lower FSIQ than TD control (Table 1).

The study was approved by the Institutional Review Board of Sheba Medical Center. After providing a complete description of the nature of this study, informed consent was obtained from all participants and from the parents of minors.

2.1.2. Philadelphia

The 22q11DS cohort was recruited from the 22q and You Center at the Children’s Hospital of Philadelphia (CHOP) as part of the Brain-Behavior and Genetic Studies of the 22q11DS, at the University of Pennsylvania and Children’s Hospital. Only individuals with standardized scores ≥ 70 on the reading section of the Wide Range Achievement Test-IV (Wilkinson and Robertson, 2006) were included. The 22q11.2 deletion status for all participants was confirmed using array CGH, SNP microarray, FISH (or MLPA). The TD participants were sampled from CHOP genotyped volunteers who underwent review of electronic medical records and a clinical assessment (Yi et al., 2015a)

The TD participants were selected at randomly after stratification by age (age range 8-21) and ethnicity as previously described (Gur et al., 2014b). They consisted of 795 participants who were similar to 22q11DS individuals both in sex distribution and parental years of education (Table 1). The Institutional Review Boards of the University of Pennsylvania and CHOP approved all study procedures. All participants or parents in the cohort provided informed assent/consent prior to participating in the study.

2.2. Psychiatric and Neurocognitive assessments

All individuals with 22q11.2DS and their main caregivers, both at the Tel Aviv and Philadelphia sites, were interviewed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime (K-SADS) (Kaufman et al., 1997). The diagnosis of a psychotic disorder was given according to the Diagnostic and Statistical Manual of mental disorders (fourth edition in Philadelphia and fifth edition in Tel Aviv). Cross-site direct observations were performed to ensure comparability of procedures.

Participants from both sites underwent comprehensive neurocognitive testing using the Penn Computerized Neurocognitive battery (CNB), a 1-h computerized cognitive battery validated using functional MRI (Roalf et al., 2014). A detailed description of the CNB is reported elsewhere (Gur et al., 2012; Gur and Gur, 2010; Moore et al., 2015). Briefly, the battery includes a training module and 14 computerized tests assessing five neurocognitive domains.

Each domain consists of two or three tests: Executive Function (composed of Abstraction and Mental-Flexibility, Attention and Working-Memory tests), Episodic Memory (composed of Verbal-Memory, Face-Memory and Spatial-Memory tests), Complex Cognition (composed of Language, Nonverbal-Reasoning and Spatial-Processing tests), Social Cognition (composed of Emotion Identification, Emotion-Differentiation and Age-Differentiation tests), and Praxis Speed (composed of Motor-Speed and Sensorimotor-Speed tests). Each test provides measures of both accuracy (number of correct responses) and speed (median time for correct responses) except Sensorimotor Processing and Motor Speed tests. Primary outcome measures are Efficiency scores of each of the CNB domains that were calculated by averaging the accuracy and speed scores of each test (Goldenberg et al., 2012; Gur et al., 2014b).

For the administration of CNB in the Tel Aviv cohort, the CNB was first translated into Hebrew and back translated to English and field tried before being administered to individuals with 22q11DS. Language Reaason (LAN) test was not fully implemented at the time of the current study, therefore it was not included in the analysis (Yi et al., 2015b). The Tel Aviv study participants underwent IQ assessment using the age appropriate version of the Wechsler test as previously described (Green et al., 2009).

2.3. Data analysis

Demographic characteristics between groups were compared using analysis of variance (ANOVA) for continuous measures, and chi-squares for categorical measures. Each test of the CNB had z-scores transformed for accuracy (number of correct responses) and speed (median time for correct responses), using TD participants from each cohort. Efficiency scores were calculated by taking the arithmetic mean of the accuracy and speed z-scores. Global neurocognitive performance (GNP) was calculated as mean of all z-scores in the battery. For consistency of interpretation, higher z-scores always reflect better performance. Response time z-scores were multiplied by −1, so that slower response time is reflected in lower z-scores. CNB z-scores less than −4 were set to a floor value of −4 to reduce the influence of outliers. These z-scores were available for accuracy and speed on 11 tests and two tests on speed only.
In order to examine the influence of group on the different of CNB domains, we conducted a two way mixed models with continuous dependent measures and distribution (ANOVA) using SPSS (Statistical Package for the Social Sciences, version 20.0 for Windows). The outcome measures included the CNB domains. The mixed model allows for subjects who are missing one or more of the CNB values to be included in the analysis, with the ability to adjust for unequal variances.

We applied the above analysis for three different samples. In each sample we compared two groups. The first sample included typically developing vs. 22q11DS. The second, 22q11DS nonpsychotic vs. 22q11DS psychotic and third for 22q11DS with psychotic disorder vs. IQ-matched WS. For effect size, Cohen's d was calculated by subtracting the groups' mean efficiency scores and dividing the difference by a pooled SD.

To detect whether the group differences in efficiency scores were derived by accuracy or speed we performed secondary analyzes comparing the means of accuracy and speed performance for each of the CNB tests between three groups of (psychotic and nonpsychotic 22q11.2DS and TD) using analysis of variance (ANOVA) with Scheffe post hoc pair-wise comparisons (see Supplement, Table S2).

3. Results

3.1. Demographic characteristic of individuals with 22q11DS

3.1.1. Tel Aviv

The 22q11DS psychotic (n=13) and nonpsychotic (n=32) subgroups were similar in mean age, parental education and sex distribution, but the 22q11DS psychotic subgroup had significantly lower FSIQ than the nonpsychotic group (66.6±11.0 vs. 78.6±10.5 respectively p=.005, Table 1). The psychotic group consisted of the following diagnoses: schizophrenia (8 cases), schizoaffective disorder (3 cases), schizophreniform disorder and psychotic disorder not otherwise specified (NOS) (1 case each).

3.1.2. Philadelphia

The demographic characteristics were similar between the psychotic (n=18) and nonpsychotic 22q11DS subgroups (n=54), with no significant difference in mean age, parental education and sex distribution (Supplementary Table 1). The psychotic group consisted of the following diagnoses: schizophrenia (9 cases), schizoaffective (6 cases), Psychotic disorder NOS (3 cases).

At the time of evaluation, 28 out of 31 22q11DS individuals with psychotic disorder across cohorts (90.3%) were on psychotropic medication (some individuals were on more than one medication). These psychoactive medications include: antipsychotics (n=21, risperidone 8, olanzapine 6, clozapine, quetiapine and chlorpromazine 2 each, fluphenazine, zuclopenthixol, amisulpride, clozapine, paliperdone and haloperidol 1 each), antidepressants (n=8, venlafaxine 3, fluoxetine 2, paroxetine, citalopram, sertraline and doxepin 1 each), mood stabilizers (n=3, valproate and carbamazepine 2 each) and anxiolytics (n=3, lorazepam 2, alprazolam 1).

3.2. Neurocognitive function in individuals with 22q11DS (n=117) vs. TD control (n=828)

In both the Tel Aviv and Philadelphia cohorts, the 22q11DS had significant or trend level for lower scores on all domains of the CNB compared to TD controls (Supplementary Appendix Table S1). Levene's test is significant for GNP between 22q11DS and typically development for the combined cohorts (F(821, 116) = 62.75, P<0.001), and the mix model analysis was adjusted for unequal variances as degrees of freedom (df) were calculated by satterwaite.

Since we found a similar pattern of differences between the 22q11DS and TD groups in both sites, we combined the Tel Aviv and Philadelphia 22q11DS cohorts for the comparison of the neurocognitive phenotype between the psychotic and nonpsychotic 22q11DS groups. This was needed to establish a sufficiently large group of psychotic individuals with 22q11DS, reducing the risk of error due to small cohorts (Figure 1).

3.3. Neurocognitive function in psychotic (n=31) vs. nonpsychotic individuals with 22q11DS (n=86)

The psychotic 22q11DS subgroup (n=31), compared to the nonpsychotic 22q11DS subgroup (n=86) had overall lower efficiency scores in the GNP score [F(1, 116)=17.55, P<.001, d=0.57], as well as in the Executive Function domain [F(1, 111)=18.12, P<.001, d=0.38], Episodic Memory [F(1, 113)=7.79, P=.008, d=0.26] and Social Cognition [F(1, 112)=7.50, P=.007, d=0.25] (Supplementary Figure 1, Appendix Table S2).

The separate accuracy and speed z-scores comparison of each task among psychotic, nonpsychotic 22q11DS and TD controls are presented in Appendix Table S2, Figure S1.

3.4. Neurocognitive function in the psychotic individuals with 22q11.DS (n=13) vs. IQ- matched individuals with WS (n=18)

We compared the 13 psychotic 22q11DS participants from the Tel Aviv site to a group of 18 individuals with WS. The two groups were matched for FSIQ [Mean ± SD = 66.6±11.0 vs. 67.1±9.8, psychotic 22q11DS vs. WS, respectively, F(1, 31)=12.34, P=.92], age [Mean ± SD = 27.3±8.8 vs. 22.81±5.5, respectively, F(1, 31)=3.02, P=.093], sex distribution (%male =50 vs. 40, respectively χ² =2.78, P=.160) and parental education [Mean ± SD = 13.40±2.3 vs. 14.02±2.7 (F(1, 30)=7.53, P=.006)]. Compared to the WS group, the 22q11DS psychotic subgroup had lower efficiency for GNP scores [F(1, 29)=13.19, P=.004, d=0.50] as well as Executive Function [F(1, 28)=7.50, P=.007, d=0.25].

![Figure 1](image-url) Comparison of the Computerized Neurocognitive Battery (CNB) neurocognitive profile, between psychotic and nonpsychotic individuals with 22q11DS in both the Tel Aviv and Philadelphia cohorts. Note: efficiency for each cognitive domain is a mean of accuracy and speed z-scores of corresponding tests in CNB. Error bars indicate standards error. The difference is significant at P<0.05.
Figure 2  Comparison in the Tel Aviv cohort of CNB efficiency scores among the psychotic 22q11DS subgroup, the nonpsychotic 22q11DS subgroup and Williams Syndrome. Note: GNP = global neurocognitive performance. Efficiency for each cognitive domain is a mean of accuracy and speed z-scores of corresponding tests in the Computerized Neurocognitive Battery. Error bars indicate standard error. The difference is significant at $P < 0.05$.

$F(1, 29) = \ldots$, $P = 0.023$, $d = 0.39$] and Episode Memory $[F(1, 29) = 16.27, P = 0.008$, $d = 0.55$] domains (Figure 2).

4. Discussion

To characterize the cognitive phenotype of 22q11DS psychotic disorders, we collected data on the neurocognitive profile in two cohorts of individuals with the deletion. We found that in both the Tel Aviv and Philadelphia cohort, individuals with 22q11DS and a psychotic disorder, compared with nonpsychotic individuals with 22q11DS, had lower GNP as well as relative deficits in executive functions, episodic memory and social cognition. Validation of the specificity of effects to the 22q11DS psychosis phenotype was found by comparing the cognitive profile of the Tel Aviv 22q11DS psychotic subgroup to an IQ-matched group of individuals with WS.

Deficits in areas of executive functioning, including working memory, attention and strategy formation, have been described in psychotic patients with 22q11DS (Chow et al., 2006; van Amelsvoort et al., 2004). We replicated and extended these findings showing that in two independent cohorts, the executive functioning domain, composed of abstraction and mental flexibility, attention and working memory is the most salient cognitive deficits in psychotic patients with 22q11DS. This finding is in line with the executive function deficits reported in general schizophrenia (Clark et al., 2010; Gold, 2004; Semkovska et al., 2004). Executive function is a key feature in 22q11DS individuals neurocognitive profile (Campbell et al., 2010b; Maeder et al., 2016). In a relatively large prospective study of children with 22q11DS followed from late childhood to mid-adolescence, executive dysfunction was a strong predictor for the emergence of prodromal psychotic symptoms during adolescence (Antshel et al., 2010). Additionally, another longitudinal study in 22q11DS showed that executive function deficits were associated with negative symptoms of psychosis (Schneider et al., 2014b). Neurocognitive function cannot be explained by one specific domain. Executive functions can be described as interrelated high-level cognitive processes that play a leading role in all neurocognitive domains. A neuroimaging study proposed a disruption in frontal lobe of the executive function in 22q11DS (Montjo et al., 2013).

Thus, executive dysfunction is a promising endophenotype for the emergence of psychosis in 22q11DS, and should be the focus of international multi-site studies aiming to identify the pathways leading to psychosis in 22q11DS.

Deficits in the episodic memory domain, including verbal memory and visual memory, have been described in individuals with 22q11DS (Campbell et al., 2010b; Chow et al., 2006) and in individuals with general schizophrenia (Brewer et al., 2014). In psychotic individuals with 22q11DS, we found deficits in accuracy for spatial memory and impairments in both accuracy and speed in face memory. Notably, our previous study found face memory to be one of the most pronounced deficits in 22q11DS (Gur et al., 2014b; Yi et al., 2015b). Impaired visual information processing is likely to affect interpretation of social-emotional functioning (Campbell et al., 2010a; Gur et al., 2014b).

The cognitive deficits in 22q11DS psychotic patients were also manifested in the social cognition domain, which is considered to be a major feature of schizophrenia (Corcoran et al., 2015; Heimberg et al., 1992) and has also been reported in individuals with 22q11DS (Campbell et al., 2010a; Debbané et al., 2006; Jablziowski et al., 2012). In an agreement with these findings, ToM performance was reported the best predictor of positive symptoms in 22q11DS (Jablziowski et al., 2012). Social cognition deficits are a relatively unexplored area for predicting psychosis in 22q11DS, compared to VIQ or executive function domain.

To our knowledge, this is the first study to compare the profile of cognitive deficits of patients with 22q11DS psychotic to another group of patients with IQ-matched developmental disability, WS. We found that patients with 22q11DS psychosis had more pronounced deficits in several cognitive domains including executive functions, episodic memory and GNP. These findings are comparable to the differences present between the 22q11DS psychotic and the nonpsychotic group. The fact that our findings were replicated in the comparison to WS is of importance, as it suggests that the cognitive deficits associated with 22q11DS psychosis are beyond the general and nonspecific cognitive deficits associated with 22q11DS or other genetically based neurocognitive disabilities.

Although the 22q11DS psychotic group has lower FSIQ than the nonpsychotic 22q11DS group, there was no significant difference in the complex cognition domain between the two groups. This finding indicates that notwithstanding deficits in executive functioning, episodic memory and social cognition, general reasoning and complex cognitive operations are relatively spared by the added burden of psychosis. Also, it might reflect an overall increased vulnerability in 22q11DS, as the CNB’s complex cognition tasks manifest a known impairment for nonverbal abilities (Campbell et al., 2010b; van Amelsvoort et al., 2004).
Of note, there was a stronger main effect of psychotic disorder on efficiency compared with accuracy or speed alone. Perhaps accuracy by itself has a misleading floor effect in 22q11DS. Efficiency, which incorporates scores of both accuracy and speed, seems more sensitive than accuracy or speed alone in distinguishing the 22q11.2DS psychotic individuals from nonpsychotic individuals with developmental disabilities.

4.1. Limitations

Several limitations of our study need to be considered. There are site differences for the cohorts; the mean age of the psychotic 22q11DS group in Philadelphia was 22 years, but the mean age of the 22q11DS in Tel Aviv was 27 years. Additionally, although much of the protocol of the study is quite similar between the two centers, including using the same CNB battery, there are some important methodological differences that may have affected the results. The CNB, which was developed in the Philadelphia site, was validated in hundreds of TD individuals. For adaptation of the CNB in Tel Aviv, we had a relatively small control group of TD participants. The age range in the 22q11DS psychotic group was quite large, varying from early adolescence to late adulthood and most psychotic patients used antipsychotic medications that potentially affect cognitive function. It is important to note that antipsychotic usage may have affected cognitive performance of our psychotic 22q11.2DS individuals as 90.3% of them were on antipsychotics (mostly atypical antipsychotics) during the study period. Even though limited contribution of medication to the neurocognitive dysfunction of schizophrenia has been reported in favor of atypical antipsychotic (Verhoeven and Egger, 2015), we cannot exclude this as a potential confound. Additional potential inter-site differences are in general cognitive level of the 22q11DS groups. IQ was not tested concomitantly with the CNB in Philadelphia, but was estimated based on the reading section of the Wide Range Achievement Test, which indicated that the cognitive level in the Philadelphia cohort was somewhat higher than that of the Tel Aviv cohort. Nonetheless, CNB results assessing specific neurocognitive performance in both cohorts and the GNP is a reliable proxy of FSIQ (Swagerman et al., 2016).

5. Conclusions

The present study is among few that investigated the cognitive phenotype of psychotic individuals with 22q11DS. Two independent cohorts from different countries allowed the ascertainment of a sufficiently powered sample of individuals with 22q11DS and psychosis to permit the identification of a distinctive neurocognitive deficit in psychotic individuals with 22q11DS. This finding is encouraging for the international efforts to establish multi-site collaborative research examining pathways leading to psychosis in 22q11DS. Our results indicate that a relatively short (~1 hour administration time) battery identified important cognitive deficits of psychotic patients with 22q11DS, including executive dysfunction and global neurocognitive performance deficits.

Future studies could focus on specific cognitive aspects of the clinical phenotype, mainly in executive function. Preliminary encouraging findings of cognitive remediation for executive function in 22q11DS have recently been published (Mariano et al., 2015). Future larger multi-site studies can establish additional factors and confounders such as age and the effect of medications on the cognitive deficits in psychotic patients with 22q11DS. Longitudinal large-scale studies will determine which of these cognitive deficits are candidate endophenotypes of 22q11DS psychosis that can serve as targets of preventive interventions.

Role of funding source

Research reported in this publication was supported by the Binational Science Foundation, Grant number 2011378, and by the National Institute of Mental Health of the National Institutes of Health MH087626, MH087636MH101722 and MH101719. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Contributors

All authors have participated sufficiently in the creation of the manuscript and have approved the final manuscript.

Declaration of interest statement

Donna McDonald-McGinn has given lectures on 22q11.2DS for Naterra. The remaining authors have no conflict of interest to report.

Acknowledgments

The authors are grateful to participants and their families. This work was performed in partial fulfillment of the requirements for a Ph.D. degree of Ronnie Weinberger, Sackler Faculty of Medicine, Tel Aviv University, Israel.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2016.08.003.

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