RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

Computerized Neurocognitive Profile in Young People With 22q11.2 Deletion Syndrome Compared to Youths With Schizophrenia and At-Risk for Psychosis

Paula C. Goldenberg,[1,2] Monica E. Calkins,[3] Jan Richard,[3] Donna McDonald-McGinn,[1] Elaine Zackai,[1,2] Nandita Mitra,[4] Beverly Emanuel,[1,2] Marcella Devoto,[1,2,5] Karin Borgmann-Winter,[3,6] Christian Kohler,[3] Catherine G. Conroy,[3] Ruben C. Gur,[3] and Raquel E. Gur[3]*

[1]Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[2]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[3]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[4]Department of Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[5]Department of Molecular Medicine, University of Rome La Sapienza, Rome, Italy

[6]Department of Child and Adolescent Psychiatry and Behavioral Science, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Received 2 August 2011; Accepted 14 November 2011

Adults with 22q11.2 Deletion syndrome (22q11DS) have increased prevalence of schizophrenia features. Our goal is to compare the neurocognitive profile in 22q11DS, schizophrenia and individuals at risk for schizophrenia. Twenty-one 22q11DS patients (8–32 years, mean 14.9 years, 15M, 6F) were matched to four comparison groups on age: low risk (n = 21), first-degree family members of schizophrenia patients (genetic risk, n = 20), individuals exhibiting putatively prodromal symptoms (clinical risk, n = 19), and patients with schizophrenia (n = 21). All participants received semi-structured interviews [Diagnostic Interview for Genetic Studies (DIGS) and the Structured Interview for Prodromal Syndromes (SIPS)], and a computerized neurocognitive battery (CNB) measuring the following domains: Abstraction and Mental Flexibility, Attention, Working Memory, Verbal Memory, Face Memory, Spatial Memory, Language, Spatial Processing, Sensorimotor Dexterity, and Emotion Processing. Sixty percent of 22q11DS participants met SIPS criteria for prodromal symptoms and one participant met criteria for paranoid schizophrenia. Thirty-eight percent met criteria for Depressive Disorders. All 22q11DS participants successfully completed the CNB. 22q11DS participants were significantly less accurate in nearly all domains, but had similar speed of response compared to the other groups. Their profile resembled that of the psychosis groups in accuracy and speed, except for more pronounced deficits in accuracy for face memory and emotion processing. Subthreshold psychotic symptoms are present in a high proportion of 22q11DS participants. Deficits shown in the CNB are more pronounced for accuracy than speed relative to the psychosis groups with similar profiles. Similar deficits have been described in the 22q11DS population using non-computerized measures, which require increased testing time.

How to Cite this Article:
Goldenberg PC, Calkins ME, Richard J, McDonald-McGinn D, Zackai E, Mitra N, Emanuel B, Devoto M, Borgmann-Winter K, Kohler C, Conroy CG, Gur RC, Gur RE. 2012. Computerized Neurocognitive Profile in Young People With 22q11.2 Deletion Syndrome Compared to Youths With Schizophrenia and At-Risk for Psychosis.
Am J Med Genet Part B 159B:87–93.

Key words: 22q11.2 Deletion syndrome; VCFS; schizophrenia risk; neuropsychology

INTRODUCTION

Several studies have reported increased frequency of chromosomal structural variation (deletion/duplication) in schizophrenia [International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Kirov et al., 2009]. These findings are of interest because they can illuminate molecular mechanisms for schizophrenia.

Grant sponsor: NIH; Grant numbers: MH087626, MH087636, K08-MH079364.
*Correspondence to:
Raquel E. Gur, 3400 Spruce St., 10th Floor, Gates Pavilion, Philadelphia, PA 19104. E-mail: raquel@upenn.edu
Published online 13 December 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.b.32005

The most frequent copy number variation (CNV) site is in the chromosome 22q11.2 region, observed in 0.2–0.4% of patients from the general population based CNV studies of schizophrenia [International Schizophrenia Consortium, 2008; Kirov et al., 2009; Stefansson et al., 2008]. Conversely, deletion of the 22q11.2 region is associated with velo-cardio-facial syndrome (VCFS) (MIM# 192430) or DiGeorge syndrome (MIM#188400) that confers increased risk of schizophrenia. The 22q11.2 Deletion syndrome (22q11DS) is therefore of special interest in examining the complex genetics of schizophrenia.

Early reports of increased prevalence of schizophrenia in adults with 22q11DS [Shprintzen et al., 1992; Pulver et al., 1994] were supported by linkage studies of familial schizophrenia in the general population that also found 22q11 to be a region of interest [Lasseter et al., 1995; Moises et al., 1995; Gill et al., 1996]. Psychosis is present in about 23–30% of adults with 22q11DS [Murphy et al., 1999; Bassett et al., 2005], relative to population prevalence of schizophrenia of less than 1% [McGrath et al., 2008]. The clinical presentation and course in the two groups is similar [Bassett et al., 2003].

Neurocognitive deficits are key features of schizophrenia [Saykin et al., 1991] that relate to impairment in functioning and present challenge to treatment [Saykin et al., 1994; Addington et al., 2005; Allott et al., 2011]. These deficits are evident in individuals at risk for schizophrenia and are likely part of the genetic liability to schizophrenia. Furthermore, the deficits are present in unaffected family members, at a level that is typically intermediate between the means of schizophrenia patients and community controls [Gur et al., 2007]. Such heritable neurocognitive traits are increasingly used as endophenotypes in large-scale genomic studies.

Individuals with 22q11DS have cognitive processing deficits in key domains affected in schizophrenia: working memory [e.g., Eliez et al., 2001; Campbell et al., 2006], visuospatial processing [e.g., Moss et al., 1999; Bearden et al., 2001; Niklasson et al., 2002; Antshel et al., 2008], emotion recognition [e.g., Campbell et al., 2006; Andersson et al., 2008], face memory [e.g., Andersson et al., 2008], verbal short-term memory [e.g., Campbell et al., 2006; Majerus et al., 2007], and attention/inhibition [e.g., Campbell et al., 2006; Gothelf et al., 2007]. However, integrative studies that prospectively examine patients with 22q11DS using the same measures applied in genetic studies of non-deleted schizophrenia patients and individuals at psychosis risk are limited. Such efforts are needed to advance the understanding of the genetic underpinnings of psychosis across populations.

Here we present the first findings of such a collaborative effort currently underway. The primary goal of this study is to compare the neurocognitive profile in 22q11DS to that of non-deleted persons with psychosis vulnerability (schizophrenia, prodromal symptoms, family members of individuals with schizophrenia) and healthy controls at low risk of developing schizophrenia. Cognitive neuroscience based behavioral measures of performance accuracy and response time were obtained with an efficient computerized neurocognitive battery (CNB), an instrument developed for large-scale genomic studies [Gur et al., 2001a, 2010]. The CNB was applied in multi-site family studies of schizophrenia and demonstrated heritability [Calkins et al., 2007, 2010; Gur et al., 2007]. The CNB has not been applied before to patients with 22q11DS and compared to non-deleted patients with schizophrenia and young people at risk for psychosis.

MATERIALS AND METHODS

Sample

Five groups were included in the study with a total of 102 participants. Twenty-one participants with 22q11.2 deletion were recruited through the ''22q and You Center'' at The Children's Hospital of Philadelphia. All participants in this group had a deletion of the 22q11.2 region [3 MB (18 participants), 1.7 Mb (2), atypical (1; SLC25A18-CLDN5)]. The non-deleted participants were recruited from the University of Pennsylvania Schizophrenia Research Center [Borgmann-Winter et al., 2006] and included 21 low risk participants (no putatively prodromal symptoms and no family history of psychosis in a first-degree relative), 21 patients with schizophrenia, 19 participants exhibiting prodromal symptoms (clinical risk), and 20 siblings of probands with schizophrenia (genetic risk). Among clinical risk participants, six had a first-degree relative with schizophrenia. Demographic information is provided in Table I. Participants were excluded if they were unable to read (based on WRAT standard score), had moderate intellectual disability (based on IQ clinical testing), or were non-verbal. The Wide Range Achievement Test (WRAT, Wilkinson & Robertson,

TABLE I. Demographics: Age, Sex, and Race

Study group	n	Age (in years)	Sex		Race[a]
22q11DS/22q	21	8–32 (mean 14.86, SD 6.17)	15M	6F	C(20), A(1)
Prodromal/CR	19	12–23 (mean 18.42, SD 2.87)	12M	7F	C(8), AA(8), A(1), M(2)
Schizophrenia/SCZ	21	17–25 (mean 20.95, SD 2.06)	13M	8F	C(7), AA(9), A(5)
Family member/GR	20	10–25 (mean 20.40, SD 3.86)	12M	8F	C(8), AA(10), A(1), M(1)
Low risk/LR	21	16–24 (mean 20.43, SD 1.99)	12M	9F	C(14), AA(3), A(1), M(2), H(1)
Total	102	8–32 (mean 19.01, SD 4.32)	64M	38F	C(57), AA(30), A(9), M(5), H(1)

Age: ANOVA $F = 2.65$, $P = 0.002$, 22q < all others in post hoc testing. Gender: $\chi^2 = 1.0316$, $P = 0.905$. Race: $\chi^2 = 37.5327$, $P = 0.002$.
[a]Race classification: C, Caucasian; AA, African-American; A, Asian; M, Multiracial; H, Hawaiian/Pacific Islander.

2006) was administered to all groups in this study as an estimate of IQ, which is a standard practice across disorders affecting brain function [e.g., Ahles et al., 2003; Strauss et al., 2006, p. 388].

Participants were evaluated when medically stable and medications were maintained as clinically indicated with no washout period in any of the patient groups. In the 22q11DS group five patients were on stimulants, two on antidepressants, and two on antipsychotic medications.

All procedures were approved by Institutional Review Board of the University of Pennsylvania and the Children's Hospital of Philadelphia.

Neuropsychiatric Interviews

Diagnostic and symptom information were assessed with semi-structured interviews including the Diagnostic Interview for Genetics Studies (DIGS) [Nurnberger et al., 1994] and the Structured Interview for Prodromal Symptoms (SIPS) [McGlashan et al., 2003]. For all child participants (under age 18), joint collateral/parent assessments were conducted (n = 8), additional collateral information was independently obtained from a parent (n = 7), or the collateral only was interviewed (n = 2). For all participants, including adult participants (n = 5), we incorporated information from treating physicians, psychologists, and medical records. For all informants, assessors were trained to adhere to standardized wording, but to be alert for participant misunderstanding and to re-state and explain questions as needed to ensure participant comprehension. All participants classified as clinical risk had at least one positive symptom rated 3–5 in severity or at least two negative and/or disorganized symptoms (rated 3–6 in severity) on the Scale of Prodromal Symptoms (SOPS); symptoms were present during the 6 months prior to testing. All participants were additionally assessed for current or history of a DSM-IV axis I or axis II cluster A disorder. These interviews were performed by trained interviewers and reviewed in a consensus conference to arrive at risk group determination and best estimate final diagnosis. For details regarding the clinical assessment, see Borgmann-Winter et al. [2006].

Neurocognitive Measures

Participants were administered a computerized neurocognitive "scan" previously applied to healthy individuals [Gur et al., 2001b, 2010], patients with schizophrenia [Gur et al., 2001a], and in large-scale genomic studies [Gur et al., 2007; Almasy et al., 2008]. It is an efficient test battery administered by research coordinators using portable computers. The battery includes a training module and has automated scoring with direct data downloading. The battery assesses the following domains.

Abstraction and mental flexibility (ABF). The Penn Conditional Exclusion Test presents four objects at a time, and the participant selects the object that does not belong with the other three based on one of three sorting principles. Sorting principles change, and feedback guides their identification (time: 12 min).

Attention (ATT). The Penn Continuous Performance Test uses a continuous performance test paradigm where the participant responds to seven-segment displays presented 1/sec whenever they form a digit or a letter. Working memory demands are eliminated because the stimulus is present (time: 8 min).

Working memory (WM). The Letter N-Back (LNB) [Ragland et al., 2002] presents letters for 500 msec, and the participant has an additional 2,000 msec to respond by pressing the spacebar. There are three conditions: 0-Back—press the spacebar when the letter presented is an "X"; 1-Back—press when the letter presented is the same as the previous letter; 2-Back—press when the letter presented is the same as the one just before the previous letter. Following a training period, the test presents three blocks of each condition in a pre-determined order, for a total of 135 trials. The number of correct responses is recorded as the measure of accuracy and median response times for correct responses as a measure of speed.

Verbal memory (VMEM). The Penn Word Memory Test presents 20 target words followed by an immediate recognition trial with targets interspersed with 20 distractors equated for frequency, length, concreteness, and low image ability using Paivio's norms. Delayed recognition is measured at 20 min (time: 4 min).

Face memory (FMEM). The Penn Face Memory Test presents 20 digitized faces subsequently intermixed with 20 foils equated for age, gender, and ethnicity. Participants indicate whether or not they recognize each face immediately and at 20 min (time: 4 min).

Spatial memory (SMEM). The Visual Object Learning Test presents 20 Euclidean shapes subsequently interspersed with foils immediately and at 20 min (time: 4 min).

Spatial processing (SPA). Judgment of Line Orientation is a computer adaptation of Benton's test. Participants see two lines at an angle and indicate the corresponding lines on a simultaneously presented array (time: 6 min).

Sensorimotor dexterity (SM). The participant uses a mouse to click on squares appearing at varied locations on the screen. The stimuli become progressively smaller (time: 2 min).

Emotion processing (EMO). Identification of facial affect was tested with a 40-item Emotion Intensity Discrimination Test. Each stimulus presents two faces of the same individual showing the same emotion (happy or sad) with different intensities. The participant selects the more intense expression. Sets were balanced for gender, age, and ethnicity (5 min). Recognition of facial affect was evaluated with an abbreviated (40 item) version of the Penn Emotion Recognition Test, which includes happy, sad, anger, fear, and neutral facial expressions (8 each). Stimuli are balanced for gender, age, and ethnicity.

Motor speed (MOT). The Computerized Finger Tapping Test (CTAP) measures how quickly the participant can press the spacebar using only the index finger. After a practice trial with each hand, the test presents five trials for the dominant hand alternating with five trials for the non-dominant hand. In each, the participant is asked to tap the spacebar repeatedly for 10 sec when the green "GO" screen is presented. The computer records the number of taps.

Statistical Analysis of Clinical Data

Clinical data were analyzed with statistical operations performed using STATA [StataCorp, 2007]. Demographic comparisons were performed with χ^2 and/or ANOVA analysis by age, sex, and race. CNB test results were the outcome measure analyzed by group,

where tests of performance included parametric (linear regression with covariates) and non-parametric (Kruskal–Wallis multiple pairwise comparison) analysis. Ten participants less than 12 years old were excluded from analysis of verbal reasoning and word memory domains as they performed a different test in these two areas due to educational and developmental limitations (8 participants with 22q11DS, 1 Clinical Risk, 1 Genetic Risk).

RESULTS

Semi-Structured Interviews

One 22q11DS participant did not complete the diagnostic interview but did complete the SIPS interview. Of the remaining participants with 22q11DS, one participant met threshold criteria for a diagnosis of paranoid schizophrenia. Eight participants met criteria for depression [major depressive disorder either single episode (n = 2) or recurrent (n = 3), depressive disorder, NOS (n = 2), and dysthymia (n = 1)]. None met criteria for mania or hypomania. Two participants had substance related disorders (alcohol abuse n = 1, and alcohol dependence, n = 1). Fourteen out of 20 22q11DS individuals not diagnosed with schizophrenia were classified as clinical risk. Prodromal symptomatology was as follows: one individual exhibited solely positive symptoms; two individuals showed a mixture of positive and negative/disorganized symptoms, and the remainder exhibited at least two negative and/or disorganized symptoms.

The Computerized Neurocognitive Battery (CNB)

All participants with 22q11.2 DS completed the CNB. The mean time to complete the battery was 1 hr 30 min (SD = 26 min). Eight participants with 22q11DS were unable to perform the Working Memory task as they were unable to master practice tests, in contrast to one each in the clinical risk and schizophrenia groups that were unable to either take or complete the Working Memory task.

Figures 1 and 2 provide the means of all five groups of participants on the computerized battery. The low-risk participants were used to calculate standardized *z* scores and other groups' *z* scores were calculated relative to the performance of this group. The group of participants with 22q11DS had an overall lower accuracy in comparison to the other participant groups. Regression analysis results for overall effects by domain, corrected for age, gender, race, and education level are presented in Table II. Handedness was also included as a covariate in Motor and Sensorimotor tasks; years of education were included as a covariate in the Verbal Memory and Verbal Reasoning tasks. Sensorimotor accuracy was not examined as all participants in all groups had perfect accuracy scores in this task.

Due to the high variability in age and performance, and the small sample size, the Kruskal–Wallis multiple comparison analysis for pairwise comparison was applied. Significant pairwise effects are listed in Table II, using stringent multiple comparisons levels of significance ($P \leq 0.0025$). Overall the 22q11DS group demonstrated significantly impaired accuracy relative to one or more comparison groups in all tests but Abstraction and Mental Flexibility. Their profile resembled that of the psychosis groups in accuracy, except for more pronounced deficits for face memory and emotion processing.

In contrast, the 22q11DS group did not show significantly reduced response speed in comparison with the other groups. Response speed was slowest in the schizophrenia group. These participants demonstrated significant slowing relative to comparison groups in Abstraction and Mental Flexibility, Working Memory, and Emotion Identification.

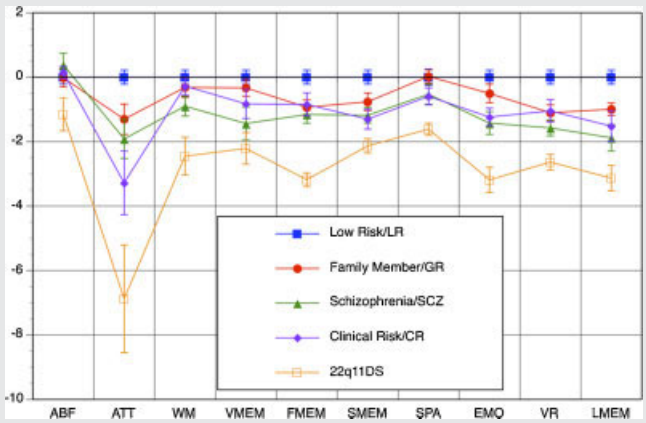

FIG. 1. Accuracy in computerized neurocognitive battery response. ABF, abstraction and mental flexibility; ATT, attention; WM, working memory; VMEM, verbal memory; FMEM, face memory; SMEM, spatial memory; SPA, spatial processing; EMO, emotion differentiation; VR, verbal reasoning; LMEM, list memory.

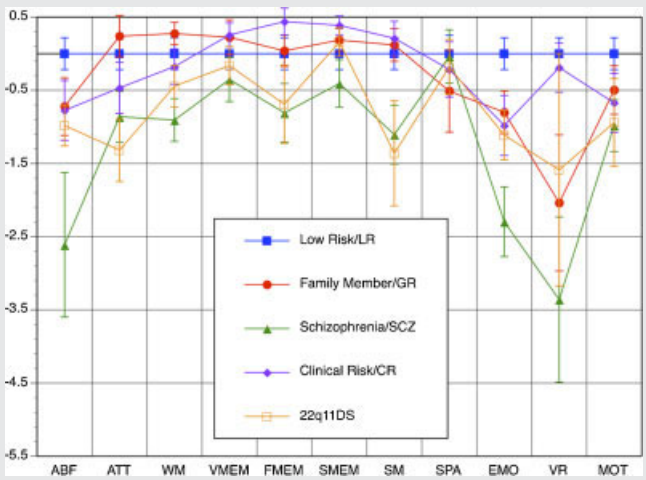

FIG. 2. Speed of correct response in computerized neurocognitive battery. ABF, abstraction and mental flexibility; ATT, attention; WM, working memory; VMEM, verbal memory; FMEM, face memory; SMEM, spatial memory; SPA, spatial processing; SM, sensorimotor; EMO, emotion differentiation; VR, verbal reasoning; MOT, finger tapping.

TABLE II. Regression Analysis: Adjusted for Age, Race, and Gender

Accuracy	F (df)	r^2	*P*	Pairwise comparison[a]
Abstraction and mental flexibility (ABF)	2.61 (7,94)	0.16	0.0164	
Attention (ATT)	9.43 (7,90)	0.42	<0.0001	**22q:**SCZ, FM, LR **PRO:**HC
Working memory (WM)	4.71 (7,84)	0.28	0.0002	**22q:**PRO, FM, LR
Verbal memory (VMEM)[b]	3.17 (8,82)	0.16	0.0035	**22q:**LR
Face memory (FMEM)	14.05 (7,93)	0.51	<0.0001	**22q:**PRO, SCZ, FM, LR
Spatial memory (SMEM)	6.03 (7,94)	0.31	<0.0001	**22q:**FM, LR **PRO:**LR, **SCZ:**LR
Spatial processing (SPA)	10.43 (7,64)	0.53	<0.0001	**22q:**FM, LR
Emotion identification (EMO)	9.68 (7,94)	0.42	<0.0001	**22q:**PRO, SCZ, FM, LR **PRO:**LR, **SCZ:**LR
Verbal reasoning (VR)[b]	13.80 (8,83)	0.57	<0.0001	**22q:**PRO, LR **SCZ:**LR, **FM:**LR
List memory (LM)	7.98 (7,94)	0.37	<0.0001	**22q:**PRO, FM, LR **SCZ:**LR
Speed				
Abstraction and mental flexibility (ABF)	2.08 (7,94)	0.13	0.0537	**SCZ:**LR
Attention (ATT)	6.30 (7,90)	0.33	<0.0001	
Working memory (WM)	3.30 (7,84)	0.22	0.0037	**SCZ:**FM
Verbal memory (VMEM)[b]	0.68 (8,82)	0.06	0.7474	
Face memory (FMEM)	2.01 (7,93)	0.13	0.1313	
Spatial memory (SMEM)	1.07 (7,94)	0.07	0.3882	
Spatial processing (SPA)	0.40 (7,64)	0.04	0.8992	
Sensorimotor (SM)[c]	1.95 (4,97)	0.11	0.3243	
Emotion identification (EMO)	5.18 (7,94)	0.28	0.0001	**SCZ:**LR
Verbal reasoning (VR)[b]	2.01 (8,76)	0.57	<0.0001	
Finger tapping (MOT)[c]	1.88 (8,91)	0.14	0.0730	

[a]Unadjusted Kruskal–Wallis one-way analysis of variance by ranks, adjusted for multiple pairwise comparisons ($P \leq 0.0025$). LR, low risk; FM, family member; PRO, prodromal/clinical risk; SCZ, schizophrenia 22q = 22q11DS groups
[b]Adjusted for education, limited to participants ≥12 years.
[c]Adjusted for handedness.

The cognitive profile of the three 22q11DS patients with atypical deletion was similar to the rest. The sample is small and it will be important to evaluate atypical deletions in larger samples.

DISCUSSION

Neuropsychiatric and neurocognitive assessment in this group of young individuals with 22q11DS supports the potential utility of prospective longitudinal studies in the context of understanding liability to schizophrenia. The clinical evaluation indicated that one 22q11DS participant had threshold features of schizophrenia, but over half of the participants with 22q11DS had significant prodromal symptoms in the SIPS interview, as has been described by other centers [Rockers et al., 2009; Stoddard et al., 2010]. Notably, this is a young sample where schizophrenia type disorder may still be evolving and longitudinal follow-up is needed to ascertain the course of psychotic symptoms in this population. The application of the SIPS in individuals with developmental disabilities requires special consideration. On the one hand, some disorganization or negative symptoms, such as deficits in "ideational richness," are evident in many individuals with 22q11DS and may not be interpretable as "prodromal" symptoms in individuals with significant developmental disabilities. On the other hand, 38% of 22q participants did not exhibit significant negative or disorganized symptoms; it is possible that those without such features have a low likelihood of developing a psychotic illness. Longitudinal follow-up will inform the predictive validity of apparently significant negative and disorganized symptoms in the 22q population.

The CNB was well tolerated by all participants, even as young as 8 years, and provided rapid assessment of several neurocognitive domains in 1.5 hr. Another advantage of the CNB is that data collection and scoring are automated and immediately available for data validation and analysis. Results with the CNB of the 22q11DS participants showed a similar neurocognitive profile to that described by others with this population using standard pencil-and-paper tasks. However, the computerized testing permits separate evaluation of accuracy and speed of performance and our study revealed that the deficits are not equal across these aspects of performance. The accuracy of the 22q11DS group overall was lower than individuals with schizophrenia. A number of CNB domains showed lower accuracy scores by the 22q11DS group than have been reported by other 22q11DS centers using traditional measures: attention [Campbell et al., 2006; Gothelf et al., 2007], working memory [Eliez et al., 2001; Campbell et al., 2006], face memory [Andersson et al., 2008], and visuospatial processing [Moss et al., 1999; Niklasson et al., 2002; Kates et al., 2007; Antshel et al., 2008]. Test procedures and comparison groups are potential sources of variability. Other significant areas of deficit found in this study include verbal reasoning and list memory. Additionally, the 22q11DS group had significantly lower performance in emotion recognition when compared to *all* of the other groups, which has also been described by other centers [Campbell et al., 2006]. Our study found less pronounced difficulty in abstract reasoning

compared to another study using the Modified Card Sorting Test [Rockers et al., 2009]. Similarly, the deficit in accuracy of verbal memory was less profound than that reported by another group [Campbell et al., 2006; Majerus et al., 2007].

In contrast to impaired accuracy, individuals with 22q11DS were less impaired in speed than patients with schizophrenia. The reduction in speed in schizophrenia has been previously described by us [Gur et al., 2001a]. As with accuracy, the profile of performance of patients with 22q11DS parallels that of the other patient and risk groups. This finding further supports the utility of the neurocognitive profile in characterizing genetically informative populations thereby rendering potential biomarkers.

The study has several limitations. Most importantly, the sample size is too small to examine the relation between neuropsychiatric and neurocognitive measures in the 22q11DS group. The experience gained from this effort has guided modifications in the CNB for younger participants with 22q11DS. For example, there was some difficulty with completion of the Letter-N-Back practice, resulting in missing data in the Working Memory task in the 22q11DS group. This task may be more developmentally appropriate and user-friendly as a 0-back and 1-back task. Additionally, very young participants in first or second grade may not be able to read sufficiently to complete word memory and verbal reasoning tasks. Interestingly, the 22q11DS group over the age of 12 performed as well as comparison groups, with exception of low risk/healthy controls, in verbal memory. This is all the more exceptional as the 22q11 group had an average of 9.7 (SD 2.6) years of completed education versus mean 11.3–13.5 in the comparison groups. Studies to date of neurocognitive processing in 22q11DS have used IQ assessment and matching. This study utilized the WRAT as an estimate of IQ and judgment of participants' ability to perform verbal tasks and participants had no mental retardation. As our focus is on brain behavior relations as part of large-scale genomic studies, we employed common research procedures across groups. With larger samples, IQ measures clinically available will enable comparison with data obtained in other research centers that assess IQ.

CONCLUSION

The results indicate the presence of psychotic symptoms and other psychopathology in youths with 22q11DS, as well as a neurocognitive profile that resembles that of patients with schizophrenia and individuals at psychosis risk. However the impairment in 22q11DS is specific for accuracy while for speed they are less impaired than patients with schizophrenia. Use of prospective neuropsychiatric and neurocognitive assessment in 22q11DS applied in the context of psychosis will permit incorporation of this population in large-scale genomic studies of brain and behavior. Longitudinal studies and correlation with neuroimaging will be required to establish pathways underlying psychosis across these groups.

ACKNOWLEDGMENTS

This study was funded by NIH grants MH087626, MH087636, and K08-MH079364.

REFERENCES

Addington J, Saeedi H, Addington D. 2005. The course of cognitive functioning in first episode psychosis: Changes over time and impact on outcome. Schizophr Res 78(1):35–43.

Ahles TA, Saykin AJ, Noll WW, Furstenberg CT, Guerin S, Cole B, Mott LA. 2003. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psychooncology 12(6):612–619.

Allott K, Liu P, Proffitt TM, Killackey E. 2011. Cognition at illness onset as a predictor of later functional outcome in early psychosis: Systematic review and methodological critique. Schizophr Res 125(2–3):221–235.

Almasy L, Gur RC, Haack K, Cole SA, Calkins ME, Peralta JM, Hare E, Prasad K, Pogue-Geile MF, Nimgaonkar V, Gur RE. 2008. A genome screen for quantitative trait loci influencing schizophrenia and neurocognitive phenotypes. Am J Psychiatry 165(9):1185–1192.

Andersson F, Glaser B, Spiridon M, Debbane M, Vuilleumier P, Eliez S. 2008. Impaired activation of face processing networks revealed by functional magnetic resonance imaging in 22q11.2 deletion syndrome. Biol Psychiatry 63(1):49–57.

Antshel KM, Peebles J, AbdulSabur N, Higgins AM, Roizen N, Shprintzen R, Fremont WP, Nastasi R, Kates WR. 2008. Associations between performance on the Rey–Osterrieth complex figure and regional brain volumes in children with and without velocardiofacial syndrome. Dev Neuropsychol 33(5):601–622.

Bassett AS, Chow EW, AbdelMalik P, Gheorghiu M, Husted J, Weksberg R. 2003. The schizophrenia phenotype in 22q11 deletion syndrome. Am J Psychiatry 160(9):1580–1586.

Bassett AS, Chow EW, Husted J, Weksberg R, Caluseriu O, Webb GD, Gatzoulis MA. 2005. Clinical features of 78 adults with 22q11 Deletion syndrome. Am J Med Genet Part A 138A(4):307–313.

Bearden CE, Woodin MF, Wang PP, Moss E, McDonald-McGinn D, Zackai E, Emannuel B, Cannon TD. 2001. The neurocognitive phenotype of the 22q11.2 deletion syndrome: Selective deficit in visual-spatial memory. J Clin Exp Neuropsychol 23(4):447–464.

Borgmann-Winter K, Calkins ME, Kniele K, Gur RE. 2006. Assessment of adolescents at risk for psychosis. Curr Psychiatry Rep 8(4):313–321.

Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL. 2007. The consortium on the genetics of endophenotypes in schizophrenia: Model recruitment, assessment, and endophenotyping methods for a multisite collaboration. Schizophr Bull 33(1):33–48.

Calkins ME, Tepper P, Gur RC, Ragland JD, Klei L, Wiener HW, Richard J, Savage RM, Allen TB, O'Jile J, Devlin B, Kwentus J, Aliyu MH, Bradford LD, Edwards N, Lyons PD, Nimgaonkar VL, Santos AB, Go RC, Gur RE. 2010. Project among African-Americans to explore risks for schizophrenia (PAARTNERS): Evidence for impairment and heritability of neurocognitive functioning in families of schizophrenia patients. Am J Psychiatry 167(4):459–472.

Campbell LE, Daly E, Toal F, Stevens A, Azuma R, Catani M, Ng V, van Amelsvoort T, Chitnis X, Cutter W, Murphy DG, Murphy KC. 2006. Brain and behaviour in children with 22q11.2 deletion syndrome: A volumetric and voxel-based morphometry MRI study. Brain 129(Pt5):1218–1228.

Eliez S, Blasey CM, Menon V, White CD, Schmitt JE, Reiss AL. 2001. Functional brain imaging study of mathematical reasoning abilities in velocardiofacial syndrome (del22q11.2). Genet Med 3(1):49–55.

Gill M, Vallada H, Collier D, Sham P, Holmans P, Murray R, McGuffin P, Nanko S, Owen M, Antonarakis S, Housman D, Kazazian H, Nestadt G,

Pulver AE, Straub RE, MacLean CJ, Walsh D, Kendler KS, DeLisi L, Polymeropoulos M, Coon H, Byerley W, Lofthouse R, Gershon E, Read CM, et al. 1996. A combined analysis of D22S278 marker alleles in affected sib-pairs: Support for a susceptibility locus for schizophrenia at chromosome 22q12. Schizophrenia Collaborative Linkage Group (Chromosome 22). Am J Med Genet 67(1):40–45.

Gothelf D, Michaelovsky E, Frisch A, Zohar AH, Presburger G, Burg M, Aviram-Goldring A, Frydman M, Yeshaya J, Shohat M, Korostishevsky M, Apter A, Weizman A. 2007. Association of the low-activity COMT 158Met allele with ADHD and OCD in subjects with velocardiofacial syndrome. Int J Neuropsychopharmacol 10(3):301–308.

Gur RC, Ragland JD, Moberg PJ, Bilker WB, Kohler C, Siegel SJ, Gur RE. 2001a. Computerized neurocognitive scanning: II. The profile of schizophrenia. Neuropsychopharmacology 25(5):777–788.

Gur RC, Ragland JD, Moberg PJ, Turner TH, Bilker WB, Kohler C, Siegel SJ, Gur RE. 2001b. Computerized neurocognitive scanning: I. Methodology and validation in healthy people. Neuropsychopharmacology 25(5): 766–776.

Gur RE, Nimgaonkar VL, Almasy L, Calkins ME, Ragland JD, Pogue-Geile MF, Kanes S, Blangero J, Gur RC. 2007. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. Am J Psychiatry 164(5):813–819.

Gur RC, Richard J, Hughett P, Calkins ME, Macy L, Bilker WB, Brensinger C, Gur RE. 2010. A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: Standardization and initial construct validation. J Neurosci Methods 187(2):254–262.

International Schizophrenia Consortium. 2008. Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature 455(7210):237–241.

Kates WR, Krauss BR, Abdulsabur N, Colgan D, Antshel KM, Higgins AM, Shprintzen RJ. 2007. The neural correlates of non-spatial working memory in velocardiofacial syndrome (22q11.2 deletion syndrome). Neuropsychologia 45(12):2863–2873.

Kirov G, Grozeva D, Norton N, Ivanov D, Mantripragada KK, Holmans P, Craddock N, Owen MJ, O'Donovan MC. 2009. Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. Hum Mol Genet 18(8):1497–1503.

Lasseter VK, Pulver AE, Wolyniec PS, Nestadt G, Meyers D, Karayiorgou M, Housman D, Antonarakis S, Kazazian H, Kasch L, et al. 1995. Follow-up report of potential linkage for schizophrenia on chromosome 22q: Part 3. Am J Med Genet 60(2):172–173.

Majerus S, Van der Linden M, Braissand V, Eliez S. 2007. Verbal short-term memory in individuals with chromosome 22q11.2 deletion: Specific deficit in serial order retention capacities? Am J Ment Retard 112(2): 79–93.

McGlashan T, Miller T, Woods S, Rosen J, Hoffman R, Davidson L. 2003. Structured interview for prodromal syndromes, Version 4.0. New Haven, CT: Prime Clinic Yale School of Medicine.

McGrath J, Saha S, Chant D, Welham J. 2008. Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30: 67–76.

Moises HW, Yang L, Li T, Havsteen B, Fimmers R, Baur MP, Liu X, Gottesman II. 1995. Potential linkage disequilibrium between schizophrenia and locus D22S278 on the long arm of chromosome 22. Am J Med Genet 60(5):465–467.

Moss EM, Batshaw ML, Solot CB, Gerdes M, McDonald-McGinn DM, Driscoll DA, Emanuel BS, Zackai EH, Wang PP. 1999. Psychoeducational profile of the 22q11.2 microdeletion: A complex pattern. J Pediatr 134(2): 193–198.

Murphy KC, Jones LA, Owen MJ. 1999. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch Gen Psychiatry 56(10): 940–945.

Niklasson L, Rasmussen P, Oskarsdottir S, Gillberg C. 2002. Chromosome 22q11 deletion syndrome (CATCH 22): Neuropsychiatric and neuropsychological aspects. Dev Med Child Neurol 44(1):44–50.

Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry 51(11):849–859, discussion 863–864.

Pulver AE, Nestadt G, Goldberg R, Shprintzen RJ, Lamacz M, Wolyniec PS, Morrow B, Karayiorgou M, Antonarakis SE, Housman D, et al. 1994. Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. J Nerv Ment Dis 182(8):476–478.

Ragland JD, Turetsky BI, Gur RC, Gunning-Dixon F, Turner T, Schroeder L, Chan R, Gur RE. 2002. Working memory for complex figures: An fMRI comparison of letter and fractal n-back tasks. Neuropsychology 16(3): 370–379.

Rockers K, Ousley O, Sutton T, Schoenberg E, Coleman K, Walker E, Cubells JF. 2009. Performance on the Modified Card Sorting Test and its relation to psychopathology in adolescents and young adults with 22q11.2 deletion syndrome. J Intellect Disabil Res 53(7):665–676.

Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P. 1991. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch Gen Psychiatry 48(7):618–624.

Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC. 1994. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch Gen Psychiatry 51(2):124–131.

Shprintzen RJ, Goldberg R, Golding-Kushner KJ, Marion RW. 1992. Late-onset psychosis in the velo-cardio-facial syndrome. Am J Med Genet 42(1):141–142.

StataCorp. 2007. Stata statistical software: Release 10. College Station, TX: StataCorp LP.

Stefansson H, Rujescu D, Cichon S, Pietilainen OP, Ingason A, Steinberg S, Fossdal R, Sigurdsson E, Sigmundsson T, Buizer-Voskamp JE, Hansen T, Jakobsen KD, Muglia P, Francks C, Matthews PM, Gylfason A, Halldorsson BV, Gudbjartsson D, Thorgeirsson TE, Sigurdsson A, Jonasdottir A, Bjornsson A, Mattiasdottir S, Blondal T, Haraldsson M, Magnusdottir BB, Giegling I, Moller HJ, Hartmann A, Shianna KV, Ge D, Need AC, Crombie C, Fraser G, Walker N, Lonnqvist J, Suvisaari J, Tuulio-Henriksson A, Paunio T, Toulopoulou T, Bramon E, Di Forti M, Murray R, Ruggeri M, Vassos E, Tosato S, Walshe M, Li T, Vasilescu C, Muhleisen TW, Wang AG, Ullum H, Djurovic S, Melle I, Olesen J, Kiemeney LA, Franke B, Sabatti C, Freimer NB, Gulcher JR, Thorsteinsdottir U, Kong A, Andreassen OA, Ophoff RA, Georgi A, Rietschel M, Werge T, Petursson H, Goldstein DB, Nothen MM, Peltonen L, Collier DA, St Clair D, Stefansson K. 2008. Large recurrent microdeletions associated with schizophrenia. Nature 455(7210):232–236.

Stoddard J, Niendam T, Hendren R, Carter C, Simon TJ. 2010. Attenuated positive symptoms of psychosis in adolescents with chromosome 22q11.2 deletion syndrome. Schizophr Res 118(1–3):118–121.

Strauss E, Sherman EMS, Spreen O. 2006. A compendium of neuropsychological tests: Administration, norms, and commentary. New York, NY: Oxford University Press.

Wilkinson GS, Robertson GJ. 2006. Wide Range Achievement Test—Fourth edition. Lutz, FL: Psychological Assessment Resources. WRAT4 Introductory Kit.