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

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### Abstract

**Objective**—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.

**Methods**—Twenty-one 22q11DS patients (8y-32y, mean 14.9y, 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.

**Results**—60% of 22q11DS participants met SIPS criteria for prodromal symptoms and one participant met criteria for paranoid schizophrenia. 38% 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.

**Conclusion**—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.

## Keywords

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; Kirov and others 2009; Stefansson and others 2008]. These findings are of interest because they can illuminate molecular mechanisms for schizophrenia. 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 and others 2009; Stefansson and others 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 [Pulver and others 1994; Shprintzen and others 1992] were supported by linkage studies of familial schizophrenia in the general population that also found 22q11 to be a region of interest [Gill and others 1996; Lasseter and others 1995; Moises and others 1995]. Psychosis is present in about 23–30% of adults with 22q11DS [Bassett and others 2005; Murphy and others 1999], relative to population prevalence of schizophrenia of less than 1% [McGrath and others 2008]. The clinical presentation and course in the two groups is similar [Bassett and others 2003].

Neurocognitive deficits are key features of schizophrenia [Saykin and others 1991] that relate to impairment in functioning and present challenge to treatment [Addington and others 2005; Allott and others 2011; Saykin and others 1994]. 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 and others 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., Campbell and others 2006; Eliez and others 2001], visuospatial processing [e.g., Antshel and others 2008; Bearden and others 2001; Moss and others 1999; Niklasson and others 2002], emotion recognition [e.g., Andersson and others 2008; Campbell and others 2006], face memory [e.g., Andersson and others 2008], verbal short-term memory [e.g., Campbell and others 2006; Majerus and others 2007], and attention/inhibition [e.g., Campbell and others 2006; Gothelf and others 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 and others 2001a, 2010]. The CNB was applied in multi-site family studies of schizophrenia and demonstrated heritability [Calkins and others 2007; Calkins and others 2010; Gur and others 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 103 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 (3MB [18 participants], 1.7Mb [2], atypical [1] (SLC25A18-CLDN5)). The non-deleted participants were recruited from the University of Pennsylvania Schizophrenia Research Center [Borgmann-Winter and others 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 1. 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 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 and others 2003; Strauss and others 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 5 patients were on stimulants, 2 on antidepressants, and 2 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 was assessed with semi-structured interviews including the Diagnostic Interview for Genetics Studies (DIGS) [Nurnberger and others 1994] and the Structured Interview for Prodromal Symptoms (SIPS) [McGlashan and others 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 and others [2006].

**Neurocognitive Measures**—Participants were administered a computerized neurocognitive “scan” previously applied to healthy individuals [Gur and others 2001b], patients with schizophrenia [Gur and others 2001a], and in large-scale genomic studies [Almasy and others 2008; Gur and others 2007]. 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 minutes).

**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 minutes).

**Working memory (WM) [Gur and others 2010]:** The Letter N-Back (LNB) [Ragland and others 2002] presents letters for 500 ms, and the participant has an additional 2000ms 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 minutes (time: 4 minutes).

**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 minutes (time: 4 minutes).

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

**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 minutes).

**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 minutes).

**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 minutes). 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 10s 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  $\chi^2$  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 twenty 22q11DS individuals not diagnosed with schizophrenia were classified as clinical risk. Prodromal symptomatology was as follows: 1 individual exhibited solely positive symptoms; 2 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 Deletion Syndrome completed the CNB. The mean time to complete the battery was 1 hour 30 minutes (SD = 26 minutes). 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 2. 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 pair-wise comparison was applied. Significant pair-wise effects are listed in Table 2, 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.

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 and others 2009; Stoddard and others 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 computerized neurocognitive battery (CNB) was well tolerated by all participants, even as young as 8 years, and provided rapid assessment of several neurocognitive domains in 1.5 hours. 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 and

others 2006; Gothelf and others 2007], working memory [Campbell and others 2006; Eliez and others 2001], face memory [Andersson and others 2008], and visuospatial processing [Antshel and others 2008; Kates and others 2007; Moss and others 1999; Niklasson and others 2002]. 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 and others 2006]. Our study found less pronounced difficulty in abstract reasoning compared to another study using the Modified Card Sorting Test [Rockers and others 2009]. Similarly, the deficit in accuracy of verbal memory was less profound than that reported by another group [Campbell and others 2006; Majerus and others 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 and others 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.

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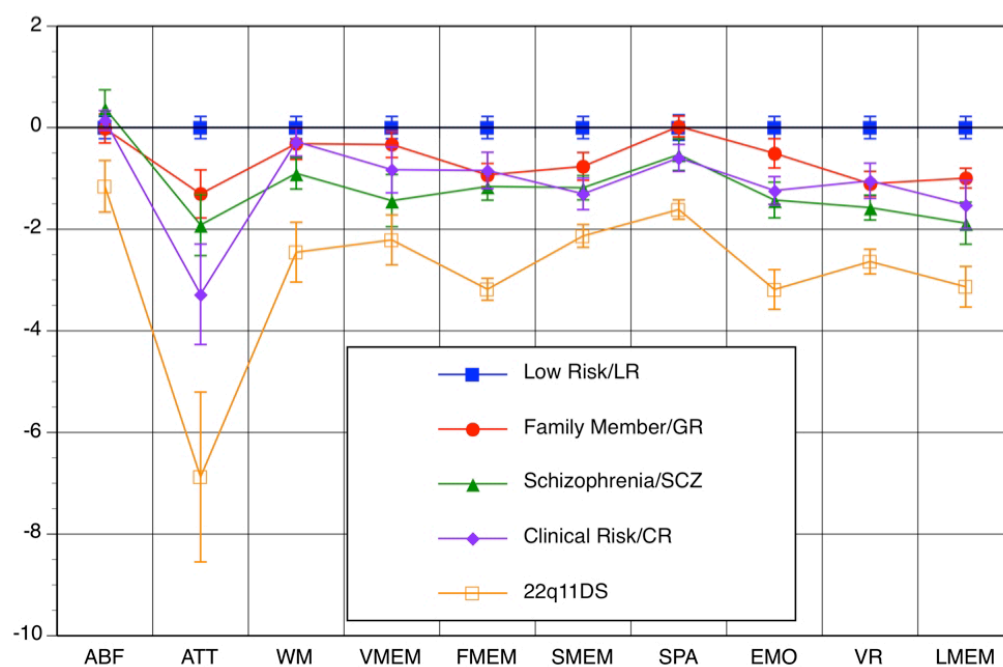
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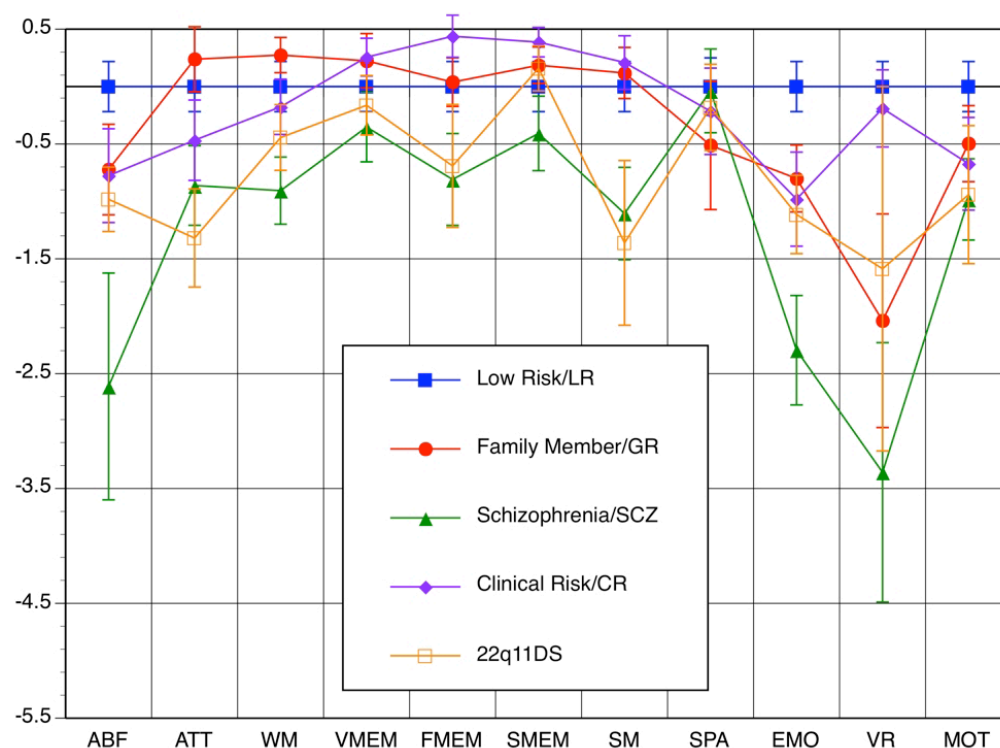


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**Figure 1. Accuracy in Computerized Neurocognitive Battery Response**  
*ABF* Abstraction and Mental Flexibility, *ATT* Attention, *WM* Working Memory, *VMEM* Verbal Memory, *FMEM* Face Memory, *SMEM* Spatial Memory, *SPA* Spatial Reasoning, *EMO* Emotion Differentiation, *VR* Verbal Reasoning, *LMEM* List Memory



**Figure 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 Reasoning, *SM* Sensorimotor, *EMO* Emotion Differentiation, *VR* Verbal Reasoning, *MOT* Finger Tapping

**Table 1**

Demographics: Age, Sex, and Race

Study Group	n	Age (in years)	Sex	Race <sup>I</sup>
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 20.4, 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)

<sup>I</sup> Race classification: C=Caucasian AA=African American A=Asian M=Multiracial H=Hawaiian/Pacific Islander

Age: ANOVA  $F=2.65$   $p=0.002$  22q<all others in post-hoc testing

Gender:  $\chi^2=1.0316$   $p=0.905$

Race:  $\chi^2=37.5327$   $p=0.002$



Table 2

Regression Analysis: Adjusted for age, race and gender

Accuracy	F	df	r <sup>2</sup>	p	Pairwise Comparison <sup>a</sup>
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 <b>PRO:HC</b>
Working Memory (WM)	4.71	(7,84)	0.28	0.0002	22q:PRO, FM, LR
Verbal Memory (VMEM) <sup>c</sup>	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 <b>PRO:LR SCZ:LR</b>
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 <b>PRO:LR SCZ:LR</b>
Verbal Reasoning (VR) <sup>c</sup>	13.80	(8,83)	0.57	<0.0001	22q:PRO, LR SCZ:LR <b>FM:LR</b>
List Memory (LM)	7.98	(7,94)	0.37	<0.0001	22q:PRO, FM, LR SCZ:LR
Speed	F	df	r <sup>2</sup>	p	Pairwise Comparison <sup>a</sup>
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) <sup>c</sup>	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) <sup>b</sup>	1.95	(4,97)	0.11	0.3243	
Emotion Identification (EMO)	5.18	(7,94)	0.28	0.0001	SCZ:LR
Verbal Reasoning (VR) <sup>c</sup>	2.01	(8,76)	0.57	<0.0001	
Finger Tapping (MOT) <sup>b</sup>	1.88	(8,91)	0.14	0.0730	

<sup>a</sup>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

<sup>b</sup> Adjusted for handedness

<sup>c</sup> Adjusted for education, limited to participants  $\geq 12$  years