Impact of Psychiatric Comorbidity and Cognitive Deficit on Function in 22q11.2 Deletion Syndrome

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ABSTRACT

Objective: Presence of psychiatric comorbidity is associated with poor functioning and is an important consideration in treatment. Many individuals with 22q11.2 deletion syndrome (22q11DS) develop comorbid psychiatric disorders, yet its pattern and impact on functioning have not been formally investigated. In this cross-sectional study, we examined the relationship between comorbid psychopathology and neurocognitive deficits and their association with global functioning. We hypothesized that higher psychiatric burden and psychosis-spectrum features would be associated with reduced functioning and increased neurocognitive deficits.

Method: The cohort included 171 individuals with 22q11DS and mean (SD) age of 17.4 (8.1) years, recruited from a tertiary children's hospital and nationally through social media between September 2010 and December 2013. Psychiatric diagnoses and functioning were assessed using semistructured interviews and the Global Assessment of Functioning (GAF) scale, respectively. On the basis of psychopathology and number of comorbid diagnoses, participants were assigned to unaffected (n = 32), nonpsychosis spectrum (n = 24), nonpsychosis spectrum-plus (n = 15), psychosis spectrum (n = 29), and psychosis spectrum-plus (n = 71) groups. Executive function, episodic memory, complex cognition, social cognition, and praxis speed were assessed using a computerized neurocognitive battery (CNB). Cognitive profile and GAF scores were compared among the groups, and the association of GAF with cognitive performance and psychopathology was examined.

Results: We observed high rates of comorbid psychiatric disorders. Approximately 50% of the participants had ≥ 2 diagnoses. Psychosis spectrum disorders were most frequently comorbid with other disorders. GAF score was progressively worse with increased psychiatric burden. Mean (SD) GAF score for the unaffected group (81.1 [8.9]) was significantly different from those of nonpsychosis spectrum (68.6 [12.1]), nonpsychosis spectrum-plus (63.4 [8.8]), psychosis spectrum (58.7 [13.1]), or psychosis spectrum-plus (55.5 [13.3]) ($P < .05$) groups. All groups performed poorly and were comparable to each other on the CNB ($P = .273$). Notably, verbal memory ($P = .003$), spatial processing ($P = .001$), and parent education level ($P < .001$) were significantly associated with GAF.

Conclusions: Individuals with 22q11DS have high rates of comorbid psychiatric disorders and diffuse cognitive deficits regardless of psychiatric burden. Those with psychotic spectrum disorders and comorbid psychiatric disorders are at an increased risk for poor overall functioning.

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Chromosome 22q11.2 deletion syndrome (22q11DS) occurs in approximately 1/4,000 live births[1] and is characterized by physical and neuropsychiatric features.[2] Developmental delays and borderline intellectual functioning are common and necessitate early intervention and school support.[3–5] Most affected children develop multiple psychiatric disorders including attention-deficit/hyperactivity disorder (ADHD) and anxiety spectrum and mood spectrum disorders.[6] Notably, up to 30% of affected individuals develop psychotic disorders[7] compared to about 10% in other genetic syndromes with developmental delays.[8] Psychiatric comorbidities in children and adolescents are common and associated with more severe disease course, differential treatment response, and poor functioning.[9] As many as 42% of patients with 22q11DS have been reported to have comorbid psychiatric disorders,[10] yet the pattern and impact on functioning have not been previously examined. Furthermore, their relationship to neurocognitive function remains unknown.

Studies of neurocognitive processes can elucidate the underlying neural substrates and lead to better identification of at-risk populations. The neurocognitive profile in 22q11DS includes deficits in executive function,[11,12] social cognition,[13,14] nonverbal memory,[15] working memory,[16] and visual-spatial function.[17,18] Most studies examining the relationship between psychopathology and cognition have focused on psychosis, reporting impairments in verbal learning, executive function, and social cognition.[19–21] Notably, a decline in verbal IQ has been associated with the emergence of psychotic disorders.[22,23] Studies examining the effect of nonpsychosis spectrum disorders on functioning found that anxiety and depressive symptoms are predictive of worse adaptive functioning.[24,25] Findings on the association of full-scale IQ and psychopathology are inconsistent, with some reporting a correlation between them,[26,27] while others do not.[28,29] Similarly, there have been inconsistent reports on the association between IQ and functional outcome. Deficits in social cognition have been associated with poor functioning.[14] Because neurocognitive deficits and psychiatric burden can negatively impact functioning, a better understanding of these phenotypes may improve clinical care.

Clinical Points

- Psychiatric comorbidity is common in individuals with 22q11.2 deletion syndrome, being present in approximately 50% of cases.
- Psychosis spectrum features and anxiety disorders are most frequently comorbid with other disorders, and clinicians should give particular consideration when assessing these domains.
- Poorer global functioning is associated with psychiatric comorbidity and psychosis spectrum features.
- Interventions targeting certain cognitive domains such as verbal memory, spatial processing, and social cognition may improve overall functioning.

We characterized a large cohort of individuals with 22q11DS, enabling investigation of these relationships. The Penn Computerized Neurocognitive Battery (CNB)[30] was applied to examine domains commonly affected in 22q11DS. Recently, we reported that neurocognitive age based on CNB performance relative to chronological age in 22q11DS was significantly delayed compared to individuals without 22q11DS but with developmental delays.[31] Here, we evaluated the pattern of comorbid psychiatric disorders in 22q11DS, hypothesizing that those with greater psychiatric burden would have poorer functioning and neurocognitive deficits. Additionally, we investigated the association of global functioning with multiple domains of neurocognitive performance and different classes of psychopathology.

METHOD

Study Population

The sample is drawn from a prospective study, Brain-Behavior and Genetic Studies of the 22q11DS, at the University of Pennsylvania and Children's Hospital of Philadelphia (CHOP).[10] The current study was conducted using the cross-sectional data from 171 participants (age range, 8–47 years; mean age = 17.44 years, SD = 8.1). Participants with 22q11DS and who were ≥ 8 years old were recruited from the 22q and You Center at CHOP and nationally through social media between September 2010 and December 2013. Inclusion criteria were ability to provide informed consent/assent, English proficiency, medical stability, and IQ > 70 by available records and IQ proxy > 70 based on the reading section of the Wide Range Achievement Test-4 (WRAT-4).[32] Exclusion criteria were pervasive developmental disorder or IQ < 70 and medical disorders that may affect brain function (eg, uncontrolled seizures, head trauma, tumor in central nervous system, or infections). To increase the reliability of the assessments and generalizability of psychotic features to the population without 22q11DS, we excluded those with pervasive developmental disorder or IQ < 70.[33] A total of 261 individuals with 22q11DS were screened at the time of the current study, and 27 were excluded due to moderate to severe intellectual disability; another 29 were excluded due to unstable medical conditions, and 2 participants were excluded due to pervasive developmental disorder diagnosis. For this report, only participants with complete psychiatric and neurocognitive data were included (n = 171). Participants' deletion status was confirmed using multiplex ligation-dependent probe amplification.[34] Of the 171 participants, 154 had typical 3 mega base (Mb) pair deletion and 9 had 1.5–1.7 Mb atypical deletions. Deletion size could not be determined for 8 participants, but the presence of a deletion was confirmed by fluorescent in situ hybridization.

Psychopathology and Global Assessment of Functioning (GAF)

Each participant underwent psychiatric and cognitive assessments, taking approximately 4 hours to complete. While 90% of participants finished the assessments on the same day, about 10% completed the assessments over a 2-day period. Psychopathology was assessed with the Kiddie-Schedule for Affective Disorders and Schizophrenia,[35] Structured Interview for Prodromal Syndromes (SIPS),[36] and the psychotic and mood differential diagnoses modules of the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[37] To reduce time burden, only sections for ADHD, mood disorders, generalized anxiety, separation anxiety, and obsessive-compulsive disorder from the K-SADS were included. As previously described,[10] positive, negative, and disorganized symptoms were rated on a 7-point scale (0: "absent"; 1: "questionably present"; 2: "mild"; 3: "moderate"; 4: "moderately severe"; 5: "severe but not psychotic"; and 6: "severe and psychotic"). Prodrome diagnoses were given for at least 1 positive symptom rated ≥ 3 or at least 2 negative and/or disorganized symptoms rated ≥ 3. Psychosis spectrum disorders included the prodrome and psychotic disorders. Participants aged 8–10 years were assessed with collateral/parent interviews and participants aged 11–14 years with independent proband and collateral/parent interviews. Interview information and medical records were presented for a case conference in which consensus symptom ratings and diagnoses were reached by at least 2 doctoral-level clinicians (J.J.Y., M.E.C., C.G.K., and R.E.G.).

The SIPS Global Assessment of Functioning (GAF)[36] was applied to evaluate level of function in social, occupation, and school domains along with the severity of psychiatric symptoms. Its values range from 1 to 100, and lower scores indicate worse functioning.[38] GAF was also determined in the consensus diagnosis conference. The institutional review boards of the University of Pennsylvania and CHOP approved all procedures. Participants and parents provided informed consent/assent prior to participating in the study.

Assignment of Psychopathology Groups

As our assessment interviews for most psychopathology domains were designed to provide psychiatric diagnoses based on *DSM-IV* criteria, a categorical rather than dimensional approach was used to assign the psychopathology groups.[39] On the basis of the nature of psychopathology (nonpsychosis spectrum vs psychosis spectrum) and level of psychiatric comorbidity, each participant was assigned to 1 of 5 mutually

exclusive groups: (1) unaffected—patients with no psychiatric diagnosis; (2) nonpsychosis spectrum—patients with ADHD anxiety disorders, and mood disorders; (3) nonpsychosis spectrum-plus—patients with 2 or more nonpsychotic spectrum disorders; (4) psychosis spectrum—patients with prodrome or psychotic disorders; and (5) psychosis spectrum-plus—patients with psychosis spectrum disorders and 1 or more nonpsychotic disorders.

Computerized Neurocognitive Battery

The CNB[30] includes 14 computerized tests assessing 5 neurocognitive domains: executive function, episodic memory, complex cognition, social cognition, and praxis speed. Each domain consists of 2 (praxis speed) or 3 (all others) tests: executive function—abstraction and mental flexibility, attention, and working memory; episodic memory—verbal memory, face memory, and spatial memory; complex cognition—language, nonverbal reasoning, and spatial processing; social cognition—emotion identification, emotion differentiation, and age differentiation; and praxis speed—motor speed and sensorimotor speed.

For each task, *z* scores for accuracy (number of correct responses) and speed (median time for correct responses) were calculated using typically developing participants, matched demographically from the Philadelphia Neurodevelopment Cohort.[40] Efficiency scores were calculated by taking the arithmetic mean of the accuracy and speed *z* scores.

Statistical Analysis

All data analyses were conducted using SAS version 9.4 (SAS Institute Inc; Cary, North Carolina). Categorical and continuous variables were analyzed using Fisher exact test and analysis of variance, respectively. Mean GAF scores across psychopathology groups were analyzed using analysis of covariance and post hoc Tukey-Kramer honest significant difference test. Sex was entered as a covariate because of the known sex differences in cognitive performances[40] and our study groups being unbalanced for sex ($P = .02$). CNB *z* scores less than −4 were set to a floor value of −4 to reduce the undue influence of outliers. Efficiency scores of CNB domains were analyzed using linear mixed model (PROC MIXED procedure). Each analysis included fixed effects for cognitive tests, psychopathology group, and the interaction terms. The random effect for subject accounted for the repeated measurements from each subject. Missing CNB values (2.5% of unaffected, 2.7% of nonpsychosis spectrum, 1.3% of nonpsychosis spectrum-plus, 4.1% of psychosis spectrum, and 7.2% of psychosis spectrum-plus) were excluded from the analysis. The mixed model allows for subjects to be included who are missing 1 or more of the CNB values. To better understand the association between cognitive performance and GAF, a stepwise regression analysis was performed using efficiency scores for each CNB test (14 variables), WRAT-4 standard score, and parent education level (average of school years completed by 2 parents) as explanatory variables and GAF as a dependent variable (PROC GLMSELECT procedure). Additionally, to examine the associations between different classes of psychopathology and GAF, the second stepwise regression analysis was performed using the presence and absence of 4 different classes of psychopathology (ADHD, anxiety disorders, mood disorders, and psychosis spectrum disorders) as explanatory variables and with the cognitive performance variables identified from the first regression analysis in the model. The cutoff for both entry and exit from the model was set at $P < .25$, and K-fold cross-validation (random block, with $K = 5$) was performed.[41]

RESULTS

Demographic Characteristics of Psychopathology Groups

Demographic information for psychopathology groups is presented in Table 1. All variables except sex were comparable across groups. In the total sample, males were slightly overrepresented (54.4% vs 45.6% [females]). Male participants represented higher proportions in the nonpsychosis spectrum, psychosis spectrum, and psychosis spectrum-plus groups (66.7%, 65.5%, 59.2%) compared to the unaffected and nonpsychosis spectrum-plus groups (34.4% and 33.3%, $P = .02$). The majority of participants were white. Parent education level and the WRAT-4 standard scores were comparable across groups.

Prevalence of Psychiatric Disorders per Psychopathology Groups

In the entire cohort (Table 1), ADHD was the most common disorder (37.4%), followed by generalized anxiety disorder (17.5%), anxiety disorder not otherwise specified (NOS) (17.1%), and major depressive disorder (12.3%). Bipolar I disorder was rare at < 1%. Of 100 participants with psychosis spectrum disorders (58.5%), prodrome was the most common (50.3%), followed by schizophrenia (4.7%).

The nonpsychosis spectrum group largely consisted of ADHD (54.2%) and anxiety NOS (25.0%); similarly, the majority of the nonpsychosis spectrum-plus group consisted of ADHD (66.7%), generalized anxiety disorder (46.7%), and anxiety NOS (40.0%). The psychosis spectrum group predominately included prodrome (79.3%); the majority of psychosis spectrum-plus consisted of ADHD (57.8%) and prodrome (88.7%).

Pattern of Comorbid Psychiatric Disorders

A Venn diagram (Figure 1) depicts the pattern of comorbidity among disorders. Sixty-nine participants met criteria for any anxiety disorders (black ellipse), 64 met criteria for ADHD (green ellipse), 31 for any mood disorders (blue ellipse), and 100 for psychosis spectrum disorders (red ellipse).

Of 69 participants in the anxiety spectrum, 10.1% had only anxiety disorders, while 39.1% had 1 other comorbid disorder and 57.7% had ≥ 2 comorbid disorders (see Supplementary eTable 1 at Psychiatrist.com). Of 64 participants with ADHD, 20.3% had only ADHD, while 40.6% had 1 other comorbidity and 39.1% had ≥ 2 comorbidities. Notably,

Table 1. Demographic Characteristics and Prevalence of Psychiatric Disorders Among Psychopathology Groups

Characteristic	Total Sample, N = 171 (100%)	Unaffected, n = 32 (18.7%)[a]	Nonpsychosis Spectrum, n = 24 (14.0%)[b]	Nonpsychosis Spectrum-Plus, n = 15 (8.8%)[c]	Psychosis Spectrum, n = 29 (17.0%)[d]	Psychosis Spectrum-Plus, n = 71 (41.5%)[e]	*P* Value[f]
Age, mean (SD)	17.44 (8.1)	19.81 (10.7)	17.53 (10.4)	19.95 (7.0)	16.04 (5.8)	16.37 (6.5)	.17
Sex, n (%)							.02
Male	93 (54.4)	11 (34.4)	16 (66.7)	5 (33.3)	19 (65.5)	42 (59.2)	
Female	78 (45.6)	21 (65.6)	8 (33.3)	10 (66.7)	10 (34.5)	29 (40.9)	
Race, n (%)							.45
White	147 (86.0)	30 (93.8)	22 (91.7)	12 (80.0)	25 (86.2)	58 (81.7)	
African American	14 (8.2)	1 (3.1)	2 (8.3)	3 (20.0)	3 (10.3)	5 (7.0)	
American Indian	1 (0.6)	0 (0)	0 (0)	0 (0)	1 (3.5)	0 (0)	
Asian/Pacific Islander	2 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.8)	
> 1	7 (4.1)	1 (3.1)	0 (0)	0 (0)	0 (0)	6 (3.5)	
Parent education, mean (SD), y	14.48 (2.2)	15.21 (2.2)	14.32 (2.2)	14.79 (2.9)	13.57 (2.0)	14.52 (2.0)	.07
WRAT-IV, mean (SD)[g]	89.87 (13.6)	92.97 (14.2)	87.96 (12.8)	90.6 (13.0)	90.66 (13.9)	88.63 (13.7)	.58
Unaffected, n (%)	32 (18.7)	32 (100)	0	0	0	0	
Nonpsychosis spectrum, n (%)[h]							
ADHD	64 (37.4)	0	13 (54.2)	10 (66.7)	0	41 (57.8)	
Anxiety disorder NOS	29 (17.1)	0	6 (25.0)	6 (40.0)	0	17 (23.9)	
GAD	30 (17.5)	0	1 (4.2)	7 (46.7)	0	22 (31.0)	
SAD	16 (9.4)	0	0	1 (6.7)	0	15 (21.1)	
OCD	12 (7.0)	0	0	2 (13.3)	0	10 (14.1)	
Mood disorder NOS	3 (1.8)	0	0	0	0	3 (4.2)	
Depressive disorder NOS	4 (2.3)	0	0	0	0	4 (5.6)	
Dysthymia	2 (1.2)	0	0	1 (6.7)	0	1 (1.4)	
Major depressive disorder	21 (12.3)	0	3 (12.5)	6 (40.0)	0	12 (16.9)	
Bipolar I disorder	1 (0.6)	0	1 (4.2)	0	0	0	
Psychosis spectrum, n (%)							
Prodrome[i]	86 (50.3)	0	0	0	23 (79.3)	63 (88.7)	
Psychosis NOS	3 (1.8)	0	0	0	3 (10.3)	0	
Schizoaffective	1 (0.6)	0	0	0	1 (3.5)	0	
Schizophrenia	8 (4.7)	0	0	0	1 (3.5)	7 (9.9)	
Delusional	2 (1.2)	0	0	0	1 (3.5)	1 (1.4)	

[a]Participants with no psychiatric diagnosis.
[b]Participants with ADHD, anxiety disorders, and mood disorders.
[c]Participants with ≥ 2 nonpsychosis spectrum disorders.
[d]Participants with prodrome or psychotic disorders.
[e]Participants with psychosis spectrum disorders and ≥ 1 nonpsychosis spectrum disorders.
[f]*P* values for age, parent education and WRAT-4 are determined by analysis of variance; gender and race by Fisher exact test.
[g]Standard score from reading segment of WRAT-4.
[h]Diagnoses were based on *DSM-IV* criteria.
[i]Prodrome indicates subthreshold psychotic symptoms based on Structured Interview for Prodromal Syndromes.
Abbreviations: ADHD = attention-deficient/hyperactivity disorder, GAD = generalized anxiety disorder, NOS = not otherwise specified, OCD = obsessive-compulsive disorder, SAD = separation anxiety disorder, WRAT-4 = Wide Range Achievement Test-4.

relative to other disorders, the mood disorder spectrum had the largest proportion (51.6%) with ≥ 2 comorbidities, and the psychosis spectrum disorders had the largest proportion (29.0%) with only psychosis spectrum disorders.

Psychosis spectrum disorders were the most commonly comorbid disorder given any other disorders (eTable 1). Among participants with ADHD, 64.1% also had psychosis spectrum disorders; among those with anxiety spectrum, 69.6% had psychosis spectrum, and among mood spectrum, 64.5% had psychosis spectrum. Anxiety spectrum was also a common comorbidity, as 50.0% and 64.5% of participants with ADHD and mood spectrum, respectively, had a comorbid anxiety disorder.

Comparison of Mean GAF Scores Across Psychopathology Groups

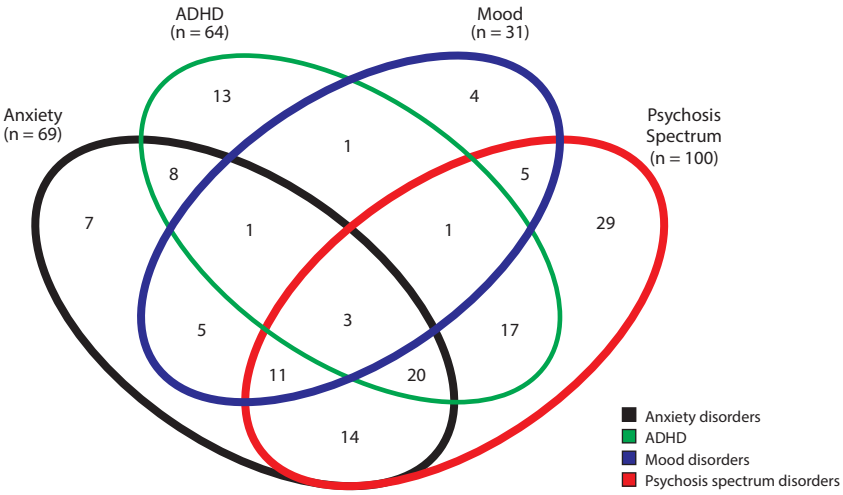
Mean GAF scores among psychopathology groups were compared (Figure 2). For the entire cohort, the mean (SD) GAF score was 63.4 (15.3) and decreased progressively from the unaffected (81.1 [8.9]) to nonpsychosis spectrum (68.6 [12.1]), nonpsychosis spectrum-plus (63.4 [8.8]), psychosis spectrum (58.7 [13.1]), and the psychosis spectrum-plus (55.5 [13.3]) groups.

There was a significant group effect on GAF scores ($P < .001$) with sex as a covariate. The result was unchanged ($P < .001$) even after excluding those with psychotic disorders, a subset of psychosis spectrum with the worst GAF (mean [SD] GAF score = 43.1 [14.5]). Pairwise comparison showed that GAF score was significantly higher in unaffected compared to the nonpsychosis spectrum ($P = .002$) and all other groups ($P < .001$). GAF score was also significantly higher in nonpsychosis spectrum compared to psychosis spectrum ($P = .03$) and higher in nonpsychosis spectrum compared to psychosis spectrum-plus ($P < .001$).

CNB Profile Across Psychopathology Groups

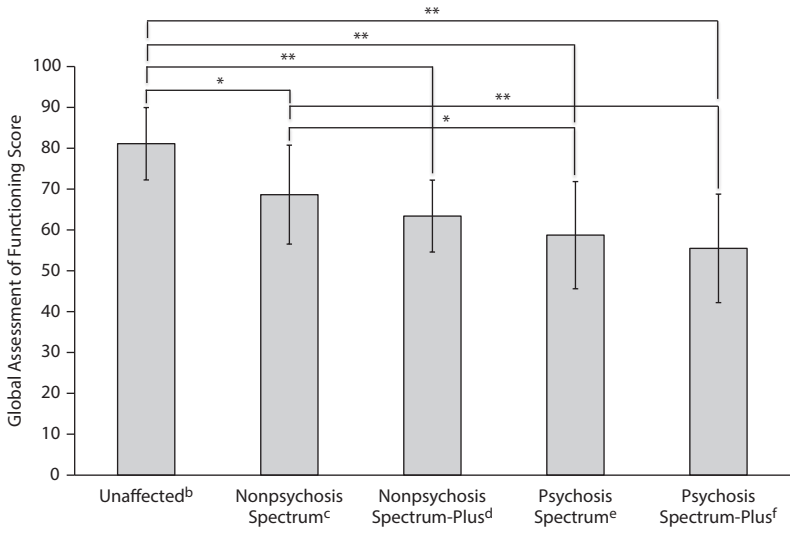
CNB efficiency scores for neurocognitive domains showed that all groups had deficits, with a mean *z* score range of −0.5 (praxis speed) to −1.4 (social cognition) (Figure 3). There was no significant main effect by group ($F_{4,161} = 1.30$, $P = .273$), group × performance ($F_{48,161} = 0.9$, $P = .661$), sex ($F_{1,161} = 3.03$, $P = .084$), group × sex ($F_{4,161} = 0.42$, $P = .792$) or

Figure 1. Venn Diagram Depicting Overlapping Psychiatric Diagnoses in 22q11.2 Deletion Syndrome[a]



[a]Anxiety disorders include generalized anxiety, obsessive-compulsive disorder, separation anxiety and anxiety disorder-not otherwise specified; mood disorders include major depressive disorder, bipolar disorder, dysthymia, depression-not otherwise specified, and mood disorder-not otherwise specified; psychosis-spectrum disorders include prodrome, psychosis-not otherwise specified, schizoaffective disorder, schizophrenia, and delusional disorder.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 2. Comparison of Mean Global Assessment of Functioning Scores Based on Psychopathology Groups[a]



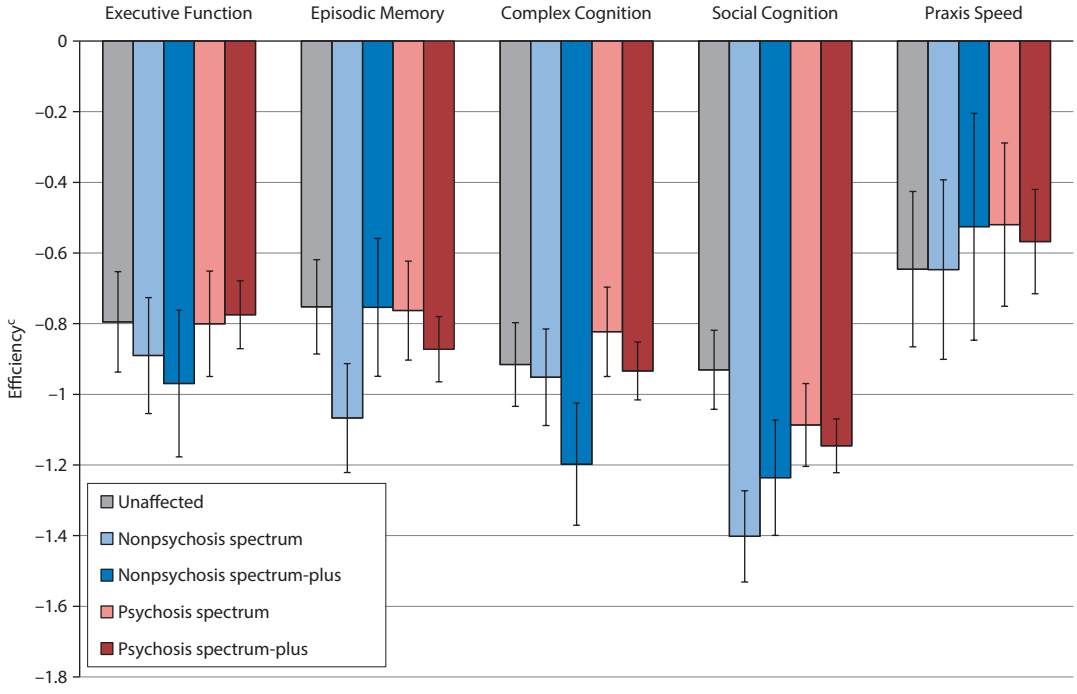
[a]*P* values are generated from post hoc Tukey-Kramer honest significant difference test.
[b]Participants with no psychiatric diagnosis.
[c]Participants with attention-deficit/hyperactivity disorder, anxiety disorders, and mood disorders.
[d]Participants with ≥ 2 nonpsychosis spectrum disorders.
[e]Participants with prodrome or psychotic disorders.
[f]Participants with psychosis-spectrum disorders and ≥ 1 nonpsychosis spectrum disorders.
*$P < .05$. **$P < .001$.

group × sex × performance ($F_{48,161} = 0.97$, $P = .528$) on CNB profile.

Association of CNB Performances and Different Classes of Psychopathology to GAF

In the initial stepwise regression analysis, 14 CNB efficiency scores, standard reading score of WRAT-4, and parent education level were entered as independent variables. Verbal memory, spatial processing, and parent education level remained in the model (Table 2), and together they explained 12.7% of variance in GAF score. The second stepwise regression analysis was performed using the presence or absence of 4 different classes of psychopathology as independent variables. The 3 variables (verbal memory,

Figure 3. Comparison of Neurocognitive Profile Among Psychopathology Group[a,b]



[a]No significant main effect was found in a linear mixed model analysis for group ($F_{4,161} = 1.30$, $P = .273$) or group × efficiency ($F_{48,161} = 0.9$, $P = .661$) terms.
[b]The nonpsychosis spectrum group included participants with attention-deficit/hyperactivity disorder, anxiety disorders, and mood disorders. The nonpsychosis spectrum-plus group included participants with ≥ 2 nonpsychosis spectrum disorders. The psychosis spectrum group included participants with prodrome or psychotic disorders. The psychosis spectrum-plus group included participants with psychosis spectrum disorders and ≥ 1 nonpsychosis spectrum disorders. The unaffected group included participants with no psychiatric diagnosis.
[c]Efficiency for each cognitive domain is the mean of accuracy and speed *z* scores of corresponding tests in the computerized neurocognitive battery. Executive function consists of abstraction and mental flexibility, attention, and working memory; episodic memory consists of verbal memory, face memory, and spatial memory; social cognition consists of emotion identification, emotion differentiation, and age differentiation; and praxis speed consists of motor speed and sensorimotor speed.

spatial processing, and parent education level) identified from the initial analysis were included in the second analysis. The presence of ADHD, any mood disorders, or psychosis spectrum disorders was significantly associated with GAF. Combined with the 3 variables identified in the first stepwise regression analysis, these psychopathologies accounted for approximately 51% of the variance of GAF (Table 2).

DISCUSSION

Psychiatric comorbidity is common among children and adolescents with psychiatric disorders and has been associated with worse outcome.[42] Owing to its high prevalence of psychiatric disorders, 22q11DS is a unique genetic model for investigating development of psychopathology.[43] Despite its importance, psychiatric comorbidity has not been formally examined in 22q11DS. Here, we report on the pattern of psychiatric comorbidities, their impact on global functioning and association with neurocognitive performance in a large cohort of patients with 22q11DS.

To characterize the effect of psychiatric burden on functioning, we compared the global functioning and neurocognitive profiles among subgroups of 22q11DS participants classified based on psychopathology and comorbidity. As our cohort excluded those participants with severe intellectual disability and pervasive developmental disorder, our findings cannot be generalized to individuals with 22q11DS in the lower end of the intellectual functioning range.

Similar to others,[6] we found a high prevalence of psychiatric disorders in our cohort. The predominant disorders were ADHD (37%), anxiety disorders (50%), and psychosis spectrum features (50%). As 22q11DS confers one of the highest genetic risks for schizophrenia,[44] it is unsurprising that a large proportion of our cohort was identified as at risk for psychosis. The predictive validity of the SIPS in 22q11DS has not yet been demonstrated, so it remains to be seen what proportion of those identified as at risk will eventually develop psychotic disorders. Nevertheless, our recent analysis found that it is a sensitive instrument in eliciting and capturing the psychosis phenomenon in 22q11DS.[45] Approximately 8% of our cohort had psychotic disorders, and this lower rate is likely due to the comparatively younger age of our cohort.

Notably, 50% of participants had ≥ 2 disorders, underscoring the complexity of psychiatric phenotype in

Table 2. Association of Neurocognitive Performances and Psychopathology to Global Assessment of Functioning[a]

	Coefficients			Model			
Variable	β	*t*	*P*	R^2	ΔR^2	*F*	*P*
Selected explanatory variables from initial stepwise regression[b]							
Verbal memory	2.557	2.31	.022	0.068	0.068	8.96	.003
Spatial processing	2.435	1.91	.058	0.107	0.039	7.26	.001
Parent education level	1.007	1.67	.098	0.127	0.020	5.84	<.001
Selected explanatory variables from second stepwise regression[c]							
Psychosis spectrum	−16.992	−8.69	<.001	0.427	0.3	81.06	<.001
Mood disorders	−3.053	−4.58	<.001	0.495	0.068	18.42	<.001
ADHD	−3.559	−1.81	.072	0.507	0.012	3.28	.072

[a]Entry and exit from the model in both analyses were set at $P < .25$.
[b]Initial stepwise regression analysis was performed using 14 efficiency scores from the computerized neurocognitive battery, parent education level (average school years completed by 2 parents), and standard score from reading section of Wide Range Achievement Test-4 as explanatory variables and Global Assessment of Functioning score as dependent variable.
[c]Second stepwise regression analysis was performed using the presence or absence of 4 different classes of psychopathology (ADHD, anxiety disorders, mood disorders, or psychosis spectrum disorders) as explanatory variables. Three variables (verbal memory, spatial processing, and parent education level) identified in the initial analysis were included in the second regression model.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

22q11DS and importance of controlling for psychiatric comorbidities in future studies. For clinicians, it would be important to assess different domains of psychopathology and recognize that comorbidities are particularly common in 22q11DS. The pattern of comorbidity in 22q11DS is complex, as individuals are susceptible to many disorders. A recent study[29] found that 37.5% of those with ADHD had at least 1 anxiety disorder. We found similarly high overlap between ADHD and anxiety disorders: 50% of those with ADHD also had anxiety disorders. Utilizing our larger sample size, we also examined comorbidity pattern of mood and psychosis spectrum disorders. Given any one disorder, psychosis spectrum disorders were the most commonly comorbid disorder. As the majority of psychosis spectrum conditions in the current sample are prodrome, this finding suggests that psychosis risk is associated with the presence of other psychiatric disorders and supports previous studies that have identified baseline anxiety and depressive symptoms as predictive of psychosis.[46]

In the population without 22q11DS, the comorbidity pattern differs depending on the index psychiatric disorder. In children and adolescents with ADHD, behavioral disorders such as oppositional defiant and conduct disorders are most commonly comorbid.[47] In the current study, we did not assess for oppositional defiant disorder or conduct disorder and therefore could not examine this particular relationship. In adolescents without 22q11DS who have mood disorder, the most common comorbid disorder is anxiety disorder, and the presence of psychiatric comorbidity is associated with increased impairment.[48] Similarly, we found high comorbidity between mood and anxiety disorders in 22q11DS. Of 69 participants with anxiety disorders, 20 (28.9%) had mood disorders, and of 31 participants with mood disorder, 20 (64.5%) had anxiety disorders. In the population without 22q11DS, the most common comorbidities among those meeting the schizophrenia prodrome criteria appear to be major depressive disorder and cannabis dependence.[49] In the current study, we found that 48% and 41% of 22q11DS participants with psychosis spectrum disorders had comorbid anxiety and ADHD, respectively. Commensurate with prior reports,[6] we found substance use disorders to be uncommon in our cohort (1.2%) and are therefore, unlikely to be a comorbid psychiatric disorder. As the prevalence of psychiatric disorders varies with age,[19,22,27] more comprehensive understanding of the relationship among disorders will be achievable via longitudinal studies, and it would be important to also assess the effect of psychiatric burden longitudinally.

Because the severity of psychiatric symptoms is considered in GAF scoring, it was not surprising that there was reduced global functioning with increased psychiatric burden. Compared to the unaffected group, all other groups had lower GAF scores. Groups with comorbid disorders had lower function than their respective counterparts without comorbid disorders. The psychosis spectrum groups had lower functioning than the nonpsychosis spectrum groups, even after exclusion of a subset with psychotic disorders. Previous studies[24,25] reported that high anxiety and depressive symptoms are associated with reduced adaptive function. However, these studies did not examine functioning across psychopathology or comorbidity. Therefore, our study extends previous findings and suggests that those with psychosis spectrum disorders are at increased risk for low overall functioning. Although our consensus GAF rating procedure most likely increased the reliability of GAF scores, the GAF scale employed in the current study does not provide measures for different functional domains. Future studies may employ more comprehensive functional measures and assess for potential confounders such as utilization of mental health services, family burden, and school support.

Regardless of psychopathology group, participants had impaired neurocognitive function, with differences

ranging from moderate for praxis-speed to large for social cognition. As in previous 22q11DS studies, social cognition performance was particularly impaired.[11,13,14] Notably, the unaffected group performed just as poorly as the other groups. Taken together, our findings suggest that 22q11DS confers generalized cognitive deficit across multiple domains regardless of additional psychiatric burden. While certain domains may be more susceptible to decline during conversion to psychosis, cross-sectionally, there seems to be no specific domain linked to nonpsychosis spectrum versus psychosis spectrum group. A large within-subject variability for some tests has been reported in 22q11DS,[12,29] and we may not have had sufficient power to detect a difference across groups. Given the complexity of neurocognitive phenotypes in 22q11DS, it would be informative to further characterize this variability. We found no difference in the proxy of IQ (ie, reading segment score of WRAT-4) across groups. Since reading ability is a relative strength in 22q11DS,[5,50] our method would most likely have overestimated the actual IQ. The lack of formal IQ scores is a limitation of the current study and precluded us from examining the association between psychopathology and IQ. We plan to address this potential issue in a future study.

We found that verbal memory, spatial processing, and parent education level were significantly associated with the global functioning, explaining 12.7% of GAF score. The presence of ADHD, mood disorder, and psychosis spectrum disorders along with verbal memory, spatial processing, and parent education in the same model accounted for 50.7% of GAF score. As severity of psychiatric symptoms is considered in GAF scoring, we expected that a high proportion of GAF scores would be explained by the presence of psychopathologies. Extrinsic factors such as level of school support and opportunities for socialization as well as intrinsic factors such as resilience most likely contribute to the overall functioning, which future studies could measure. Notably, presence of anxiety disorder was not significantly associated with GAF score, perhaps because we did not assess for specific phobia and social anxiety, the most frequent types of anxiety disorders in 22q11DS.[6] Previous 22q11DS studies[15,16,51–53] have reported relatively worse performances in visual-spatial and nonverbal domains than in other cognitive domains. The relationship between these domains may be of particular interest in 22q11DS. Our finding suggests that interventions aimed at improving verbal memory and spatial processing might lead to better functioning in 22q11DS. Parent education level is most likely correlated with socioeconomic status and better access to resources, which may explain its relationship with global function.[54]

In conclusion, our findings highlight several important areas for clinicians. We found that up to half of individuals with 22q11DS have 2 or more psychiatric disorders and that reduced global functioning was associated with increased psychiatric comorbidity and psychosis spectrum disorders. Additionally, regardless of the psychiatric burden, 22q11DS was associated with diffuse cognitive deficits, with relative strength in praxis speed and weakness in social cognition. Treatment of psychiatric disorders, which are undertreated in 22q11DS,[10] and interventions aimed at improving verbal memory, spatial processing, and social cognition may offer useful approaches to improve overall functioning.

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Previous presentation: The study findings were presented at the 9th Biennial International 22q11.2 Deletion Syndrome Meeting; June 19–22, 2014; Mallorca, Spain.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Impact of Psychiatric comorbidity and Cognitive Deficit on Function in 22q11.2 Deletion Syndrome

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List of Supplementary Material for the article

1. eTable 1 Comorbid psychiatric disorders given indicated diagnosis

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Supplementary eTable 1. Comorbid psychiatric disorders given indicated diagnosis

Given diagnosis	N	Diagnosis alone (%)	Diagnosis plus ADHD (%)	Diagnosis plus Anxiety (%)	Diagnosis plus Mood (%)	Diagnosis plus Psychosis-Spectrum (%)
ADHD	64	13 (20.3)	n/a	32 (50.0)	6 (9.4)	41 (64.1)
Anxiety	69	7 (10.1)	32 (46.4)	n/a	20 (29.0)	48 (69.6)
Mood	31	4 (13.0)	6 (19.4)	20 (64.5)	n/a	20 (64.5)
Psychosis Spectrum	100	29 (29.0)	41 (41.0)	20 (20.0)	20 (20.0)	n/a

Anxiety includes Generalized Anxiety, Obsessive-Compulsive Disorder, Separation Anxiety and Anxiety Disorder-Not Otherwise Specified; Mood includes Major Depressive Disorder, Bipolar Disorder, Dysthymia, Depression-Not Otherwise Specified and Mood Disorder-Not Otherwise Specified; Psychosis-Spectrum includes Prodrome, Psychosis-Not Otherwise Specified, Schizoaffective Disorder, Schizophrenia and Delusional Disorder.