Subtle Cognitive Dysfunction in Nonaffected Siblings of Individuals Affected by Nonpsychotic Disorders

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Background: Previous studies have reported that as a group, individuals affected by psychotic and nonpsychotic disorders perform below norms on cognitive tests. Other studies have indicated that unaffected siblings of individuals affected by psychotic disorders also perform below norms on the same tests. We investigated cognitive performance on a large, population-based sample of individuals, affected at the time of testing by nonpsychotic disorders, and their unaffected siblings.

Methods: Subjects were taken from a population-based cohort of 523,375, 16- to 17-year-old male adolescents who had been assessed by the Israeli Draft Board. Cognitive test scores were examined in sib-pairs discordant for nonpsychotic ($n = 19{,}489$) and psychotic ($n = 888$) disorders and compared with 224,082 individuals from sibships with no evidence of mental illness.

Results: There appears to be a gradient in cognitive performance (worst to best) from individuals currently affected by psychotic illnesses (Cohen's $d = -.82$), followed by individuals currently affected by nonpsychotic illness (Cohen's $d = -.58$), unaffected siblings of individuals affected by psychotic illness (Cohen's $d = -.37$), unaffected siblings of individuals affected by nonpsychotic illness (Cohen's $d = -.27$), and members of sibships with no evidence of mental illness. Unaffected siblings of both psychotic and nonpsychotic individuals from multiple affected sibships (more then one affected sibling) had worse cognitive test scores compared with unaffected siblings from simplex sibships (only one affected sibling).

Conclusions: The results support, but do not prove, the notion that cognitive impairment in psychiatric disorders is familial and cuts across diagnostic entities.

Key Words: Cognition, nonpsychotic disorders, psychotic disorders, unaffected siblings

While cognitive impairment is more pronounced in psychotic illnesses (1), there is considerable evidence for subtle cognitive impairments in nonpsychotic disorders, including unipolar depression (2), bipolar disorder (3), anxiety disorders (4,5), posttraumatic stress disorder (PTSD) (6–8), obsessive-compulsive disorder (OCD) (9–11), personality disorders (12–15), and substance abuse (16,17). The presence of subtle neuropsychological dysfunction in both psychotic and nonpsychotic disorders was recently confirmed in two large population-based studies (18,19). Although cognitive impairments have been described repeatedly in psychotic illnesses (1) and some of the neural mechanisms of these impairments have been suggested (20), less is known about similar deficits in nonpsychotic disorders.

The cosegregation of psychotic illness and cognitive impairment within families is consistent with (but does not prove) the notion that genetic factors influence both traits, and those neuropsychological indices can be used as endophenotypes for schizophrenia and bipolar disorder (2,21–27). Furthermore, the observation that subtle neuropsychological deficits precede the manifestation of psychotic illnesses suggests that at least a portion of those impairments are not simply the result of psychotic symptom expression, psychotropic medication, or other illness sequelae and comorbidities (e.g., sleep disturbances, hospitalizations, or comorbid substance use). Rather, current models suggest that cognitive dysfunction in persons affected by psychotic illnesses is due, in part, to genetic predisposition to these illnesses (23). Currently, no comparable data exist regarding cognitive dysfunction in individuals affected by nonpsychotic disorders and the potential familiarity of this phenomenon.

The goal of this study is to examine whether cognitive dysfunction is present in unaffected siblings of individuals affected by nonpsychotic disorders, in a similar manner as it was demonstrated to be present in nonaffected siblings of individuals affected by psychotic disorders. For this purpose, we utilized the cognitive and psychopathology screening performed by the Israeli Draft Board on all male adolescents eligible for draft in the country. We previously utilized these data to demonstrate that, as a group, individuals currently diagnosed with psychotic or nonpsychotic mental illnesses have cognitive impairments (19). The current analysis focuses on the unaffected siblings of these individuals and is designed to test whether individuals at genetic risk for psychiatric illness have cognitive impairments that, albeit subtle, are robust at the population level. More specifically, we hypothesized that unaffected siblings of individuals affected by nonpsychotic mental illnesses will manifest subtle cognitive impairment. To strengthen the familial/genetic claims, we include a supplementary analysis to determine if unaffected individuals from sibships with a single affected person (simplex sibships) perform better than individuals from sibships with more then one affected person (multiplex sibships).

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Methods and Materials

The Israeli Draft Board Registry

Israeli law requires that the entire, unselected population of male adolescents between the ages of 16 and 17 undergo cognitive, medical, and psychiatric assessments of their eligibility for military service. The male adolescents also undergo a medical examination, in which the Draft Board physician takes a medical and psychiatric history and performs a physical examination.

Cognitive Assessment. The cognitive assessment includes four tests: 1) instructions test, a modified Otis-type verbal intelligence test adapted from the U.S. Army Alpha Instructions Test, which measures the ability to understand and carry out verbal instructions (score range = 0–21); 2) verbal analogies, a modified version of the similarities subtest of the Wechsler Intelligence Scales that assesses verbal abstraction and categorization (range = 0–30); 3) mathematical knowledge, which measures mathematical reasoning, concentration, and concept manipulation (range = 0–25); and 4) nonverbal analogies, a modified version of Raven's Progressive Matrices that measures nonverbal abstract reasoning and visual-spatial problem-solving abilities (range = 0–30).

Tests are progressive, beginning with relatively simple questions and becoming more difficult. Tests are group-administered and are time-limited. All scores are based on number of correct answers. The sum of the scores for the four tests forms a validated measure of general cognitive abilities (intelligence quotient [IQ]) (28), which is scored on a nine-point scale, and in this study we used this sum score as a composite measure of cognitive functioning.

Psychiatric Screening. After the cognitive assessments are performed, an interview assessing personality and behavioral traits is conducted independently by a different interviewer. The interviewers are college-aged persons who participated in a 4-month training course on the administration of the interview. The behavioral assessment includes the following subscales: 1) Social Functioning, which assesses the ability to make and keep friends; 2) Individual Autonomy, which assesses autonomy in taking action and making decisions; 3) Organizational Ability, which assesses compliance to time tables, self-mastery, and self-care; 4) Physical Activity, which assesses involvement in extracurricular physical activities; 5) Functioning, which assesess the ability to function in structured environments, such as school or at work; 6) Motivation, which assesses motivation to serve in the military; and 7) Prediction, which is the interviewer's overall prediction of the adolescent's ability to succeed in the military. Each behavioral measure is rated on a scale ranging from 1 (worst) to 5 (best): a score of 1 reflects very low levels of the trait; 3 reflects intermediate, common levels; and 5 reflects high, above-normal levels. The test-retest reliability of the behavioral assessment for inductees interviewed after several days by different interviewers is above .8, and population-based norms are available for each of the behavioral measures (29,30). These tests, which were developed by the Department of Behavioral Sciences in the Israel Defense Forces, are similar to standard psychometric and scholastic achievement tests, and the reliability and predictive power of the items are constantly monitored.

Based on the interview and on the physician's examination, adolescents suspected of suffering from behavioral disturbances or mental illness are referred for an in-depth assessment by a mental health professional, and if the adolescent warrants a psychiatric diagnosis, a board certified psychiatrist will examine him. Criteria for referral to an in-depth mental health assessment are a score of 1 on the prediction subscale, a history of psychological or psychiatric treatment, current complaints, or manifestation of behavioral abnormalities during the assessment procedure. The mental health assessment is administered using a semistructured interview performed by a clinical social worker or psychologist, who inquires about personal and family history, previous psychological and psychiatric treatments, interpersonal relationships, self-injurious and antisocial acts, and functioning within the family and in school. Based on the mental health assessment, if the clinician suspects that the adolescent suffers from psychopathology, a provisional diagnosis is suggested, and the adolescent is then referred for evaluation to a board certified psychiatrist experienced in treating adolescents. Adolescents who have previously been treated by mental health professionals or who have been hospitalized are required to present treatment summaries and/or discharge letters. Diagnoses during the time covered by this study were based on ICD-9 criteria and were divided into psychotic disorders (schizophrenia, schizophreniform disorder, brief reactive psychosis, schizoaffective disorder) and nonpsychotic diagnoses, including personality disorders (narcissistic, borderline, schizoid, avoidant, dependent, histrionic, or obsessive-compulsive personality disorders), antisocial personality disorder and substance abuse, schizophrenia spectrum personality disorders (schizotypal personality disorder and paranoid personality disorder), neurosis, anxiety disorders, mild depression, PTSD, and adjustment disorders. As the Draft Board diagnosis of major affective disorder includes affective disorders with or without psychotic features, adolescents diagnosed with major affective disorders in the Draft Board were not included in the analysis. In cases of comorbidity, the examining psychiatrist decides which diagnosis is most clinically significant, and only that diagnosis is recorded, without the comorbid condition. For a more detailed description of the Draft Board assessment procedure, see Gal (29) and Tubiana and Ben-Shachar (31).

Study Cohort

The study cohort included 523,375 male adolescents consecutively assessed by the Draft Board. Of these, 43,953 (8.4%) of the cohort members were assigned a psychiatric diagnosis by Draft Board psychiatrists. Sibships within the cohort were identified using information available from the Draft Board on the unique national identification (ID) number of the parents of cohort members. The ID number is assigned to all citizens at birth or upon immigration. The cohort included 116,779 male sibships with at least two siblings per sibship. Sibships with individuals diagnosed with organic disorders, mental retardation, and autism were removed from the analyses. Individuals in the study were divided according to their belonging to sibships with psychotic or nonpsychotic disorders and their belonging to simplex sibships (i.e., sibships with only one affected sibling) or multiplex sibships (i.e., sibships with two or more affected siblings) (Figure 1).

All of the cognitive test scores presented are from the assessments performed at age 16 to 17. Hence, the individuals in this study currently had a diagnosis of psychotic or nonpsychotic illness when they were tested, were the siblings of individuals with psychotic or nonpsychotic illness, or were individuals from sibships with no evidence of mental illness.

Statistical Analyses

Univariate analysis of covariance (ANCOVA) was used to compare the composite cognitive test score between individuals with psychotic and nonpsychotic disorders, their unaffected