Impairment of Executive Function and Attention Predicts Onset of Affective Disorder in Healthy High-Risk Twins

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ABSTRACT

Objective: To investigate whether measures of cognitive function can predict onset of affective disorder in individuals at heritable risk.

Method: In a high-risk study, 234 healthy monozygotic and dizygotic twins with and without a co-twin history of affective disorder (high- and low-risk twins, respectively) were identified through nationwide registers and assessed at baseline using the Schedules for Clinical Assessment in Neuropsychiatry, the 17-item Hamilton Depression Rating Scale (HDRS), and the cognitive tests Trail Making Test Parts A and B, the Stroop test, and the Cambridge Cognitive Examination-Revised (CAMCOR). Participants were followed longitudinally at 6-month intervals for up to 9 years and finally reassessed with a personal interview to obtain information on whether they had developed psychiatric illness. The study was conducted between 2003 and 2012.

Results: 36 participants (15.4%) developed psychiatric disorder, mainly affective and anxiety disorders (31 diagnoses) (*ICD-10*). Onset was predicted by decreased executive function as reflected by performance on the Trail Making Test A – B (hazard ratio [HR] = 1.02; 95% CI, 1.00–1.03) when adjusted for sex, age, years of education and HDRS score at baseline. Reduced global cognitive function as indicated by a lower CAMCOR score at baseline showed a trend toward an association with subsequent illness onset ($P = .08$). With regard to the 5 CAMCOR subscales, lower scores on attention (HR = 0.71; 95%, CI, 0.54–0.94) and language (HR = 0.76; 95% CI, 0.58–0.99) were significantly associated with subsequent illness onset.

Conclusions: Among healthy individuals at heritable risk for affective disorder, discrete cognitive deficits, especially within executive function and attention, seem to predict subsequent onset of affective illness.

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Unipolar and bipolar disorders can be conceptualized as disorders of brain systems regulating mood, motivation, and related cognitive, endocrine, and behavioral functions.[1] Persistent cognitive dysfunction is an important dimension of both disorders that affects clinical outcome, reducing coping skills and psychosocial function and contributing to illness progression.[2]

Studies of cognition suggest that unipolar and bipolar patients exhibit mild cognitive impairment even in the euthymic phase and that this impairment increases with the illness progression,[3–8] which may indicate a neurodegenerative component of affective disorder. It is currently unresolved whether the cognitive deficits are attributable to core mood symptoms or rather constitute a separate evolution, prognosis, and impact on functional status.[9] It is therefore possible that cognitive impairment does not only develop as part of illness progression but may in fact be present before the illness onset. This possibility raises the intriguing question whether cognitive impairments reflect neurodevelopmental changes in addition to neurodegenerative processes. To elucidate this question, prospective studies of whether cognitive function in healthy first-degree relatives of patients with affective disorders is related to subsequent illness onset would provide a particularly powerful design.[10,11] Emerging evidence suggests that healthy first-degree relatives of bipolar probands exhibit discrete deficits within executive function, verbal memory, and sustained attention compared with healthy controls with no psychiatric history in first-degree relatives.[12] Concerning unipolar disorder, there is a lack of high-risk studies investigating cognitive function in first-degree relatives of unipolar probands in adult samples. A recent review concerning cognition in depression suggests that the cognitive difficulties seen in depression may precede illness onset and contribute to neural dysfunction, based on studies of children of depressed parents.[13]

In the cross-sectional part of the present study, we showed impairment of global cognitive performance and executive function in healthy twins discordant for unipolar or bipolar disorder compared with control twins with no co-twin or first-degree relatives with psychiatric disorder.[14] In the follow-up part of the study, we found that individuals at familial risk of affective disorders were at greater risk of developing affective (or any psychiatric) disorder than individuals with no family history of psychiatric illness and at even greater risk if they were young, female, and displayed even mild subclinical depressive symptoms at baseline.[15]

The aim of the present study was to investigate whether cognitive function in a healthy, never-depressed cohort of twins at heritable risk for affective disorder can predict illness onset.

METHOD

The present study sample is part of an ongoing high-risk study investigating risk factors of affective disorder. Healthy monozygotic and dizygotic twins with and without a co-twin history of affective disorder were identified through nationwide registers. Two risk groups were identified: (1) the high-risk group comprising twins at risk of affective disorder (dizygotic or monozygotic twin, co-twin affected) and (2) the low-risk group (control

Clinical Points

- In healthy individuals at risk for affective disorders, lower cognitive performance seems to predict subsequent development of psychiatric illness.
- Based on the present findings, it is possible that cognitive impairment not only develops as part of illness progression but may in fact be present before the illness onset.
- There is a clinical need for earlier and more thorough psychiatric assessment, including neuropsychological testing, in individuals at risk for affective disorder to aid earlier diagnosis and easier admission to psychiatric treatment.

group) comprising twins at low risk of affective disorder (dizygotic or monozygotic twin, co-twin unaffected).

The Registers

The Danish Civil Registration System assigns a unique personal identification number to all Danish residents. All other Danish registers use the same unique identifier and thus Danish residents can be tracked in all the public registers through record linkage. The Danish Psychiatric Central Research Register is nationwide, with registration of all psychiatric admissions and, since 1995, outpatient hospital contacts in Denmark for the country's 5.3 million inhabitants.[16,17] From April 1969 to December 1993, diseases were classified according to the *International Classification of Diseases*, *Eighth Revision* (*ICD*-8)[18] and from January 1994 according to the *International Statistical Classification of Diseases*, *10th Revision* (*ICD-10*).[19] The Danish Twin Registry was initiated in 1953 and contains information on 75,000 twin pairs born from 1870 to 2003.[20]

The linkage. Through record linkage between the Danish Twin Register, the Danish Psychiatric Central Research Register, and the Danish Civil Register, a cohort of high-risk twins was identified. This linkage identified same-sex twin pairs in which 1 twin had been treated in a psychiatric hospital setting for an affective episode (the proband) and 1 had not been treated for affective disorder (the healthy high-risk co-twin). Probands were identified as twins who, on their first admission in the period between 1968 and 2005, were discharged from a psychiatric hospital with a diagnosis of depression or recurrent depression (*ICD*-8 codes: 296.09, 296.29; *ICD-10*-codes: F32–33.9) or a first diagnosis of manic or mixed episode of bipolar affective disorder (*ICD*-8-codes: 296.19, 296.39; *ICD-10* codes: F30-31.6, F38.00). The control twins (low-risk) were identified as 1 twin from a twin pair in which the co-twin had no known personal history (the index control twin) of hospital contact due to affective/psychiatric disorder and matched on age, sex, and zygosity for each high-risk twin.

Ethics

The Danish Ministry of Health, the Danish Scientific Ethic Committee, and the Data Inspection Agency approved the study. The study was conducted (2003–2012) in accordance with the latest version of the Declaration of Helsinki. All procedures were carried out with the adequate understanding and written informed consent of the participants.

Participants at Baseline

In total, 204 high-risk and 204 low-risk twins were invited to participate in the study. A total of 271 twins agreed to participate, and subsequently, 37 twins were excluded (mainly because of a prior or current affective episode). The 234 participants were divided into groups according to risk of affective disorder as described above. Participants and nonparticipants at baseline are described in detail elsewhere.[21]

Baseline Assessment

Participants were rated in a face-to-face interview using semistructured interviews: diagnoses were obtained using Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1.[22] All individuals with a lifetime (current or past) diagnosis of affective disorder, schizoaffective disorder, or schizophrenia according to SCAN interview were excluded from the study. The 17-item Hamilton Depression Rating Scale (HDRS)[23] was used to assess depressive symptoms. At the end of the interview, participants were interviewed about lifetime family psychiatric history of first-degree relatives based on the brief screening for family psychiatric history questionnaire described by Weissman and colleagues.[24] Socioeconomic status and education level were assessed according to the Danish Statistical Socioeconomic Classification.[25]

Cognitive Tests

Global cognitive function was assessed using the Cambridge Cognitive Examination (CAMCOG).[26] The CAMCOG is a detailed neuropsychological instrument incorporating a brief neuropsychological battery that is especially sensitive to mild cognitive dysfunction; its ability to distinguish between demented, depressed, and normal individuals has been validated.[27] The test includes subscales measuring orientation, language comprehension and expression, remote and recent memory and learning, attention, ideational thinking and ideomotor praxis, calculation, abstract thinking, and visual and tactile perception. The maximum total CAMCOG score is 105.[28] The items measuring general knowledge were not standardized for persons younger than 60 years, so these 6 items (items 166–171) were omitted in the Cambridge Cognitive Examination-Revised (CAMCOR) score, resulting in a maximum total CAMCOR score of 99. Three specific cognitive tests were used (Trail Making Test Parts A and B and the Stroop test). The Trail Making Test Part B[29] is a test of executive function, including selective and sustained attention. The Stroop test is a test of executive function, inhibitory control, and attention.[30,31] The Stroop stimuli involve, at a basic level, the ability of an individual to sort information from his or her environment and to selectively react to this information.[31]

Outcome Assessment

Onset definition, follow-up, and outcome assessment. Our outcome was onset, defined as development or occurrence of an affective disorder or other psychiatric disorder during the follow-up period. Onset was assessed with a SCAN interview at follow-up. In order to identify all individuals with a potential outcome, a multiplicity of methods was used: After baseline assessment, the participants were followed longitudinally at 6-month intervals. In order to obtain information on the development of an affective episode participants received a letter containing the 21-item Beck Depression Inventory (BDI)[32] and the Mood Disorder Questionnaire (MDQ)[33] every 6 months.

The follow-up assessment was conducted from January 1, 2010, to April 30, 2012. At follow-up, all participants underwent a telephone interview. A SCAN interview was performed if, according to the telephone interview, participants (1) had had any contact with a psychologist or psychiatrist, (2) had been on sickness leave because of personal trouble, (3) had been prescribed any psychopharmacologic medicine, (4) had answers on the questionnaires (BDI, MDQ) that raised the suspicion of onset of psychiatric disorder, or (5) received a first psychiatric diagnosis in the Danish Psychiatric Central Research Register during follow-up (these data were available, as the personal identification numbers of all participants were linked to this register).

Statistical Analyses

Multiple group comparisons were performed using 1-way analysis of variance (ANOVA) for multiple outcomes or χ^2 tests for categorical variables. All participants were followed from baseline to 9 years and censored at the time of death or withdrawal from the study. Hazard ratios (HRs) were estimated in separate models using Cox proportional hazards regression to determine significant predictors of time to onset of a psychiatric disorder. All models were adjusted for the effect of age at baseline, sex, years of education at baseline, HDRS score at baseline, and risk status and followed by backward elimination of non-significant variables. The level of significance was set at .05 (2-tailed). SPPS, version 15 for Windows (IBM) was used to create a database and to undertake the statistical analyses.

RESULTS

Participants at Follow-Up

All participants were followed from baseline for up to 9 years (mean = 7.0 [SD = 2.0] years, minimum = 0.2 years, maximum = 8.9 years). The original cohort, consisting of 234 participants (152 females and 82 males, mean age = 43.9 [SD = 13.3] years), comprised 146 high-risk twins and 88 low-risk twins. Seven participants died during the follow-up period (5 high-risk participants and 2 low-risk participants; no one died of suicide), 1 emigrated (low-risk participant), and 3 were not possible to trace (1 high-risk participant and 2 low-risk participants). The remaining 223 eligible participants were contacted by letter followed by a phone call and invited to participate in a follow-up interview. Of the 223 eligible participants, 218 participants (98%) completed the personal interview at follow-up.

Table 1. Onset of Affective Disorder or Other Disorders During Follow-Up in 36 Participants

Onset Diagnosis	No. of Diagnoses
Any mood disorder	24
Bipolar disorder	2
Depression	22
Anxiety disorder	7
Substance abuse	2
Other diagnoses[a]	3

[a]Other diagnoses: schizophrenia, personality disorder, and organic depressive disorder.

Onset of Psychiatric Illness

As can be seen from Table 1, 36 participants developed psychiatric illness during the follow-up period: 24 participants (67%) developed an affective disorder, 7 (19%) an anxiety disorder, and 5 (14%) other diagnoses. Of all participants who developed psychiatric illness during follow-up, 4 were admitted to psychiatric hospital, 21 were prescribed antidepressants, and 11 completed a course of psychotherapy.

Demographic Characteristics, Risk Status, HRSD, and Cognitive Scores at Baseline According to Onset

As can be seen from Table 2, the 36 onset participants exhibited significantly younger age, higher HRSD score, and lower CAMCOR score at baseline in univariate analyses than healthy participants. Using a χ^2 test, no significant differences were found according to zygosity (16 monozygotic and 20 dizygotic twins in the onset group and 64 monozygotic and 134 dizygotic twins in the group of healthy participants, $P = .15$) or according to whether the participants fulfilled the criteria for a lifetime minor psychiatric diagnosis at baseline according to the SCAN interview (eg, previous alcohol abuse, phobia, stress-depression/anxiety reactions) at baseline (10 participants in the onset group and 26 participants in the group of healthy participants, $P = .14$).

Baseline Trail A – B Score as a Predictor of Onset

Table 3 shows the results of a Cox regression survival analysis concerning the association between Trail A – B score (the difference between Trails A and B) at baseline and later onset of psychiatric illness. The analyses were adjusted for differences in age at baseline, sex, years of education, HRSD score, and risk status at baseline and subsequently followed by backward elimination of non-significant variables. After elimination of the variable *years of education*, a significant association between Trail A – B score at baseline and subsequent onset of psychiatric disorder was found ($P = .02$, including all high-risk participants; $P = .05$, including high-risk participants disposed to unipolar disorder only; Table 3). Onset was further significantly associated with younger age at baseline (HR = 0.96; 95% CI, 0.93–0.99; $P = .01$), higher HDRS score (HR = 1.17; 95% CI, 1.00–1.37; $P = .05$), and female sex (HR = 3.09; 95% CI, 2.6–7.59; $P = .01$) (all persons).

Table 2. Demographic and Clinical Characteristics of Participants With Onset of Psychiatric Disorders Versus Healthy Participants[a]

Characteristic at Follow-Up	Onset, n = 36 (15.4%)	Healthy, n = 198 (84.6%)	*P* Value
Risk status, high[b]/low[c], n/n			
All	31/5	115/83	
Unipolar only	24/5	86/83	
Sex, male/female, n/n			
All	6/30	76/122	.01
Unipolar only	5/24	66/103	.01
Age at baseline, y			
All	39.4 (11.4)	44.8 (13.4)	.03
Unipolar only	40.0 (11.8)	45.5 (13.5)	.04
Age at follow-up, y			
All	46.4 (11.3)	51.7 (13.7)	.03
Unipolar only	47.1 (11.7)	52.4 (13.8)	.05
Education at baseline, y			
All	12.1 (2.9)	12.9 (3.3)	.18
Unipolar only	12.2 (3.0)	12.8 (3.4)	.43
HDRS score			
All	3.9 (2.4)	2.5 (1.8)	.001
Unipolar only	3.9 (2.6)	2.3 (1.7)	.001
Cognitive measures at baseline			
Mental tracking			
Trail Making Test Part A score			
All	31.9 (11.3)	31.3 (12.2)	.80
Unipolar only	32.7 (12.0)	31.7 (12.6)	.68
Executive function			
Trail Making Test Part B score			
All	80.8 (31.6)	72.8 (29.1)	.15
Unipolar only	81.0 (29.9)	73.7 (29.6)	.24
Trail Making Test Part A – B score			
All	48.9 (30.4)	41.5 (21.2)	.08
Unipolar only	48.3 (29.4)	42.1 (21.1)	.18
Stroop and Color-words score			
All	53.5 (11.7)	52.0 (12.8)	.54
Unipolar only	53.2 (11.5)	51.6 (12.6)	.53
Stroop score			
All	0.7 (6.8)	−0.7 (10.3)	.45
Unipolar only	0.3 (6.8)	−0.8 (9.9)	.58
All cognitive domains			
CAMCOR total score			
All	92.5 (3.4)	94.1 (3.3)	.01
Unipolar only	92.4 (4.3)	94.1 (3.4)	.01
CAMCOR subscale score			
Language			
All	28.6 (1.3)	28.9 (1.3)	.22
Unipolar only	28.5 (1.5)	28.0 (1.3)	.15
Orientation			
All	9.9 (0.3)	9.9 (0.2)	.38
Unipolar only	9.9 (0.3)	10.0 (0.2)	.56
Memory			
All	23.9 (1.4)	24.2 (1.7)	.36
Unipolar only	23.9 (1.4)	24.2 (1.8)	.46
Attention			
All	8.2 (1.1)	8.5 (1.0)	.10
Unipolar only	8.3 (1.1)	8.5 (1.0)	.18
Praxis			
All	14.7 (0.6)	14.8 (1.2)	.65
Unipolar only	14.7 (0.6)	14.9 (1.3)	.57

[a]Data are presented as mean (SD) unless otherwise specified. Results are presented for participants with unipolar and bipolar disorder (all) or unipolar only.
[b]High-risk participants were monozygotic or dizygotic twins with a co-twin history of affective disorder.
[c]Low-risk participants were monozygotic or dizygotic twins without a co-twin history of affective disorder.
Abbreviations: CAMCOR = Cambridge Cognitive Examination-Revised, HDRS = 17-item Hamilton Depression Rating Scale.

Baseline CAMCOR Score as a Predictor of Onset

As can be seen from Table 3, a Cox regression survival analysis followed by backward elimination revealed no significant associations between CAMCOR score at baseline and subsequent onset of psychiatric disorder, but showed a trend toward the outcome that a lower score predicted onset ($P = .08$). Onset was significantly associated with female sex (HR = 3.26; 95% CI, 1.26–7.59; $P = .02$), younger age (HR = 0.96; 95% CI, 0.93–0.99; $P = .001$), and higher HDRS score (HR = 1.20; 95% CI, 1.01–1.38; $P = .01$).

CAMCOR Subdivided Into Cognitive Domains

The baseline CAMCOR was separated into the 5 subscales. As above, Cox regression analyses were done, and the 2 subscales significantly associated with onset are presented in Table 3. A significant association was found between a lower attention score at baseline and subsequent onset of psychiatric disorder ($P = .02$) for onset participants disposed to both unipolar and bipolar disorder but not for high-risk participants predisposed to unipolar disorder only ($P = .10$). Onset was also significantly associated with female sex (HR = 2.66; 95% CI, 1.09–6.46; $P = .03$), younger age (HR = 0.96; 95% CI, 0.93–0.99; $P = .01$), higher HDRS score (HR = 1.23; 95% CI, 1.06–1.42; $P = .01$), and less education at baseline (HR = 0.89; 95% CI, 0.79–1.00; $P = .05$) (all onset persons).

Regarding language, a borderline significant association between a lower language score at baseline and subsequent onset of psychiatric disorder was found for all high-risk participants ($P = .06$) and a significant association was found for high-risk participants predisposed to unipolar disorder only ($P = .05$). Onset was further significantly associated with female sex (HR = 3.11; 95% CI, 1.26–7.69; $P = .01$), younger age (HR = 0.96; 95% CI, 0.93–0.99; $P = .003$), unipolar risk status (HR = 1.32; 95% CI, 1.02–1.70; $P = .05$), and higher HDRS score (HR = 1.26; 95% CI, 1.08–1.47; $P = .004$) at baseline.

Entering orientation and memory, respectively, in the Cox regression model did not reveal any significant associations. Finally, the Stroop and Color-words score revealed no associations with subsequent illness onset (results not presented).

DISCUSSION

The present study suggests that, in healthy individuals at risk for affective disorders, lower cognitive performance at baseline predicted subsequent development of psychiatric illness, mainly affective and anxiety disorders. This association was significant even when corrections were made for the possible influence of subclinical depressive symptoms at baseline and the well-established risk factors of a family history of affective disorder, young age, and sex. Cognitive impairment may hence be present before onset of the affective disorder

and therefore reflect neurodevelopmental processes. The existence of such an ongoing neurodevelopmental process in healthy individuals at risk for affective disorder is further supported by our previous demonstration of decreased hippocampal volume in healthy high-risk twins from the present cohort, suggesting that hippocampal volume reduction may be a part of the diathesis.[34] The present results are in line with the results from the cross-sectional part of the study indicating that healthy individuals at risk for affective disorder exhibit discrete cognitive abnormalities concerning language processing, declarative memory, and executive function.[14] In the present follow-up part of the study, language processing (verbal fluency covers 50% of the total score on the CAMCOR language subscale) and executive function as indicated in Trail A – B, but not declarative memory, were found to be predictive of later onset.

The onset group showed significant deficits in language processing, attention, and executive function but not in motor speed. With respect to the effect size concerning the Trail Making Test Part B, every extra second to completion of the task increased the risk of subsequent onset by 2%. In other words, spending 5 seconds more on solving the task increased the risk of illness onset by 10%. This finding suggests that decreased executive performance predicted subsequent onset, results that are in line with a large meta-analysis of cognitive impairment in euthymic depressive disorder.[35] The meta-analysis demonstrated that patients exhibited pronounced deficits of executive function compared with healthy control persons and that these deficits were most common among patients with later onset depression.

Table 3. Cox Proportional Hazards Ratio (HR) Estimates for Onset of Affective Disorder According to Cognitive Measures[a]

Variable at Baseline	HR	95% CI	*P* Value
Trail Making Test score			
Part A – B			
All	1.02	1.00–1.03	.02
Unipolar only	1.02	1.00–1.04	.05
CAMCOR score			
Total			
All	0.91	0.82–1.01	.09
Unipolar only	0.92	0.82–1.07	.18
Subscale			
Attention			
All	0.71	0.54–0.94	.02
Unipolar only	0.78	0.57–1.05	.10
Language			
All	0.79	0.80–1.01	.06
Unipolar only	0.76	0.58–0.99	.05

[a]The model included the covariates risk status, age, sex, years of education, and score on the HDRS items at baseline. Risk status was high (co-twin with affective disorder) or low (co-twin without affective disorder). Results are presented for participants with unipolar and bipolar disorder (all) or unipolar disorder only.
Abbreviations: CAMCOR = Cambridge Cognitive Examination-Revised, HDRS = 17-item Hamilton Depression Rating Scale.

Comparison With Other Studies

The present study is the first high-risk study to show that discrete impairments in cognitive function predict later onset as assessed according to a diagnostic psychiatric interview. Our findings are in accordance with the results from a Swedish population-based study.[36] This study included nondepressed individuals (20–64 years) followed for 3 years. A total of 708 participants completed a cognitive test battery at baseline, of whom 164 (23.2%) met the criteria for a depression diagnosis according to questionnaires at follow-up. The study revealed that low episodic memory performance at baseline predicted depression 3 years later.[36] In the present study, memory measured by one of the subscales of CAMCOR did not predict subsequent onset; instead, the measures of executive function and attention were found to be predictive. Our results are in line with the recent demonstration of neurocognitive deficits in euthymic bipolar patients even after their first affective episode.[37] To our knowledge, no studies have investigated cognitive function in euthymic unipolar patients upon recovery from their first depressive episode.

A review of potential cognitive risk markers in children of bipolar patients identified 4 follow-up studies with different follow-up periods.[38] The review suggested that attentional and executive problems are associated with risk of mood disorder, but it was inconclusive whether these problems were associated with subsequent onset of bipolar disorder. We have not identified studies of children of unipolar patients that measure cognition. Regarding the present results, the group of onset persons predisposed to bipolar disorder (n = 7, Table 2) seems to contribute substantially to the significant difference concerning executive function and attention as seen in Table 3.

Neurocognitive function may represent an indicator of genetic risk of psychiatric disorders in general, and it may be that this risk contributes separately to cognitive function regardless of diagnoses. As described in the introduction, these deficits may constitute a separate evolution, prognosis, and impact on functional status. This could explain why not all patients suffering from severe psychiatric disorders such as schizophrenia, bipolar disorder, and severe unipolar disorders have cognitive deficits. Further, it may also explain why cognitive dysfunction is a stronger marker of familial heritability in schizophrenia than in bipolar disorder[39,40] and also seems to be a stronger vulnerability marker in bipolar disorder than in unipolar disorder. In other words, the severity of psychopathology may reflect the cognitive dysfunction in the proportion of patients suffering from these deficits. In a further search for biomarkers or genetic markers of neurodegenerative functioning, the field may therefore benefit from cooperating across diagnosis as initiated in the Cognitive Genomics Consortium (COGENT).[41] Finally, we recommend integrating other relevant risk markers of cognitive dysfunction,[42] eg, metabolic disorders, known to have both genetic overlap and equal signs of cognitive dysfunction, with the described psychiatric disorders for the purpose of exploring the genetic architecture of cognition.[41]

Strengths and Limitations

The present participation rate of approximately 98% at the follow-up interview is quite satisfactory, although 25% did not complete all the questionnaires that had been sent to them. Another strength of the study is that the use of registers required no permission from probands to contact the high-risk twins. There are also disadvantages from using registers: the diagnoses are clinical rather than research based and only a few validity studies have been conducted concerning affective diagnosis.[43] However, studies have shown that the diagnosis of affective disorder made from registers is correct in 94% of the cases when compared with *ICD-10* diagnoses made from case notes using the Operational Criteria Checklist (OPCRIT) and interviews[44] and in 86.4% of the cases when using a SCAN interview.[45] Concerning cognition, high-risk and low-risk twins were not matched on the basis of IQ, as the participants' IQ was not assessed. Instead, the results were analyzed in a regression model including years of education as an adjusting variable, and this variable may not be a sufficient substitute for an IQ score. Being broader could have optimized the cognitive test battery, and none of the newer computerized test batteries such as the Cambridge Neurological Test Automated Battery (Cambridge Cognition Ltd) or the Emotional Test Battery were included at baseline due to the time span. The CAMCOG is a structured schedule for the assessment of cognition in the elderly; it presently has limited value as a screening tool in a healthy, young population. Nevertheless, the items measuring general knowledge were omitted, as these were not standardized according to age. The remaining items can measure the more general nature of cognitive problems. In the present study, only lower scores on attention and language predicted illness onset. That may be explained by the sample size, with only 36 onset persons; thus, the broad measure of cognition represented by the total CAMCOR score showed a trend toward being significantly predictive of later onset ($P = .08$).

A strength of the high-risk design is that none of the participants were treated with psychotropic medicine previous to or at the time of the cognitive examination, thereby avoiding possible medical side-effects on cognition. Finally, it is a strength that the measures of executive function and sustained attention are predictive of onset even when adjusting for the established predictors (familial predisposition, age, sex, education) and also when including subclinical depressive scores at baseline. Subclinical depressive scores at baseline were also included in order to reduce possible influence of subclinical depressive symptoms on cognition.

Implications

The present results should be replicated in larger cohorts. Nevertheless, the findings add important support to the hypothesis that cognitive disabilities reflect ongoing neurodevelopment and neurodegenerative processes. As cognitive dysfunction is a clinically important dimension of psychiatric disorders that transcends traditional diagnostic boundaries,[2] it would be of interest to follow high-risk cohorts with a family history of both affective and psychotic disorders. Approximately 40% of patients with unipolar or bipolar disorder display cognitive dysfunction, and longitudinal studies suggest that these problems worsen over time.[8,46–49] Cognitive impairment has substantial impact on functional outcome, affecting patients' ability to work, and seems to worsen the course of illness.[50–52] Therefore, the present findings highlight a clinical need for earlier and more thorough psychiatric assessment, including neuropsychological testing, in individuals with a family history of affective disorder to aid earlier diagnosis and easier admission to psychiatric treatment.

CONCLUSIONS

This study demonstrates that cognitive dysfunction predicts subsequent onset of affective disorder in healthy individuals at heritable risk of affective disorder and indicates that discrete reduction of executive function in a high-risk cohort is part of the premorbid course of illness.

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Additional information: Through record linkage between the Danish Twin Register (http://www.sdu.dk/en/Om_SDU/Institutter_centre/Ist_sundhedstjenesteforsk/Centre/DTR/Forskning), The Danish Psychiatric Central Research Register (http://www.psykiatriskforskning.dk/registre/psykiatrisk-centralregister/), and the Danish Civil Register (http://www.cpr.dk/cpr/), a cohort of "high-risk" twins was identified. Drs Vinberg and Kessing store all linkage data.

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