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# Cognitive function in unaffected twins discordant for affective disorder

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## ABSTRACT

**Background.** Patients may present with cognitive impairment in the euthymic phase of affective disorder, but it is unclear whether the impairment is prevalent before onset of the illness. The aim of the present study was to examine the hypothesis that genetic liability to affective disorder is associated with cognitive impairment.

**Method.** In a cross-sectional high-risk case–control study, healthy monozygotic (MZ) and dizygotic (DZ) twins with (High-Risk twins) and without (the control group/Low-Risk twins) a co-twin history of affective disorder were identified through nationwide registers. Cognitive performance of 203 High-Risk and Low-Risk twins was compared.

**Results.** Healthy twins discordant for unipolar disorder showed lower performance on almost all measures of cognitive function: selective and sustained attention, executive function, language processing and working and declarative memory, and also after adjustment for demographic variables, subclinical symptoms and minor psychopathology. Healthy twins discordant for bipolar disorder showed lower performance on tests measuring episodic and working memory, also after adjustment for the above-mentioned covariables. The discrete cognitive impairment found seemed to be related to genetic liability, as the MZ High-Risk twins showed significant impairment on selective and sustained attention, executive function, language processing and working and declarative memory, whereas the DZ High-Risk twins presented with significantly lower scores only on language processing and episodic memory.

**Conclusions.** The hypothesis that discrete cognitive impairment is present before the onset of the affective disorder and is genetically transmitted was supported. Thus, cognitive function may be a candidate endophenotype for affective disorders.

## INTRODUCTION

Studies on cognition have shown that patients may present with mild cognitive impairment in the euthymic phase of unipolar and bipolar disorders and that the impairment may be linked to the progression of the affective disorder (Kessing, 1998; Ferrier & Thompson, 2002; Martinez-Aran *et al*. 2004; Thompson *et al*. 2005). The cognitive impairment may be present before the onset of the affective disorder, raising the question of whether the cognitive deficits could be an expression of a genetic predisposition to affective disorder. In a review, it was proposed that executive function and declarative memory might be candidate neurocognitive endophenotypes for bipolar disorder (Glahn *et al*. 2004). Prospective studies, measuring cognition before the onset of affective disorder, may provide information on whether

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Table 1. *Cross-sectional studies of cognitive function in first-degree relatives of probands with bipolar disorder compared to controls*

| Study | Offspring<br>Mean age<br>Male/female | Control<br>Mean age<br>Male/female | Cognitive impairment |
|---|---|---|---|
| Gourovitch *et al*. (1999) | 7 MZ twins<br>32·7<br>1/7 | 15 MZ<br>28·9<br>6/9 | Brown–Petersen Memory Task, Verbal List Learning and Wechsler Memory Scale<br>No differences on Trail A and B, Facial Recognition, Reys test, Letter Fluency, Boston naming test and WAIS-R IQ |
| Keri *et al*. (2001) | 20 first-degree<br>35·1<br>8/12 | 20<br>33·1<br>7/13 | Long Delay Recall Task<br>No differences on Wisconsin Card Sorting Test, Letter Fluency and Short Delay Recall and Recognition |
| Sobczak *et al*. (2002) | 19 first-degree<br>41·4<br>4/11 | 15<br>40·3<br>4/11 | Tower of London, Picture Learning Test and the Visual Verbal Learning Test independent of the effect of acute tryptophan depletion<br>No differences on Stroop, Working Memory, Retrieval, Dichotic Listening Task, Attentional Set Shifting |
| MacQueen *et al*. (2004) | 7 first-degree<br>22·3<br>4/7 | 7<br>22·3<br>6/1 | No differences on the Visual Backward Masking Test |
| Zalla *et al*. (2004) | 33 first-degree<br>37·3<br>13/20 | 20<br>35·1<br>7/12 | Stroop interferens<br>No differences on the Verbal Fluency Test, the Wisconsin Card Sorting Test, the Trail Making Test and WAIS-R |
| Ferrier *et al*. (2004) | 17 first-degree<br>34·8<br>7/10 | 17<br>34·2<br>7/10 | Backward Digit Span CANTAB Spatial Span, CANTAB Spatial Recognition<br>No differences on Stroop, Trail A, Trail B, Vigil, Psychomotor Performance and Rey Auditory Verbal Learning Test |
| Clark *et al*. (2005*a*, *b*) | 27 first-degree<br>43·2<br>13/14 | 46<br>39·3<br>23/23 | Intra-dimensional/extra-dimensional Shift Task<br>No differences on the Rapid Visual Information Processing, the Sustained Attention Performance and the California Verbal Learning Test |
| McIntosh *et al*. (2005) | 24 first- or second-degree<br>33·5<br>9/24 | 50<br>35·5<br>23/50 | National Adult Reading Test, Wechsler Abbreviated Scale of Intelligence, Simple and Choice Reaction Time, Digit-Symbol Substitution Test, Stockings of Cambridge Test, Extended Rivermead Behavioural Memory Test. No single neuropsychological measure was related to the liability to bipolar disorder |
| Kieseppa *et al*. (2005) | 19 (MZ 2)<br>45·8<br>13/19 | 114 (MZ 59)<br>47·8<br>55/114 | No differences on the WAIS Vocabulary test and on all the Memory tests except that female co-twins showed impairment on the California Verbal Learning Test |

MZ, monozygotic; DZ, dizygotic; WAIS-R, Wechsler Adult Intelligence Scale – Revised; CANTAB, Cambridge Neuropsychological Test Automated Battery.

the cognitive impairment is related to genetic factors and represents endophenotypes between genes and the disorder. Assessment of first-degree relatives of patients with affective disorders may therefore provide a powerful design for investigating the biological vulnerability in unipolar and bipolar disorders (Sobczak *et al*. 2000).

Nine studies measuring cognition in healthy individuals with a genetic predisposition to bipolar disorder have been published. Table 1 shows that six out of the nine studies found impairment in cognitive performance mainly on tasks concerning selective attention, inhibition and set shifting. The twin study from Finland found differences concerning only the female co-twins of bipolar twins (Kieseppa *et al*. 2005). The study mainly included dizygotic twins and the mean age (45·8 years) was above the average age of onset of bipolar disorder. The results of two studies were negative, one of them including only a few participants and, as a pilot study, only one cognitive measure was used (MacQueen *et al*. 2004). To the best of our knowledge, no studies on cognition in relatives of unipolar probands have been published and it was previously noted that there is a lack of information on the heritability, familial association and co-segregation of learning and memory symptoms related to major depression (Hasler *et al*. 2004).

Kendler *et al*. (1995) were the first to describe a study design that identified twins in four categories of risk by crossing zygosity with family history of affective disorder. This design is used in the present study to identify a sample of healthy individuals who have a higher genetic liability than the samples normally included in studies of High-Risk individuals using ordinary first-degree relatives. Based on this design, the aim of the present study was to investigate the hypothesis that genetic liability to affective disorder is associated with cognitive impairment by comparing a group of healthy twins who have a co-twin history of affective disorder (the High-Risk group) with a group of healthy twins without (the Low-Risk group). To our knowledge, this is the first study that also investigates cognitive function in first-degree relatives of patients with unipolar disorder.

## METHOD

### The registers

The Danish Civil Registration System assigns a unique personal identification number to all residents in Denmark. This number is linked to information on name, address and date of birth; information on death, emigration and immigration is also recorded in the system. 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 out-patient hospital contacts in Denmark for the country's 5·3 million inhabitants (Munk-Jorgensen & Mortensen, 1997). From April 1969 to December 1993, diseases were classified according to the ICD-8 (WHO, 1967) and from January 1994 according to the ICD-10 (WHO, 2005). The Danish Twin Registry was initiated in 1953 and contains information on 75 000 twin pairs born from 1870 to 2003. The completeness varies with the birth cohort and is approximately 70% for the period before and close to 100% for the period after the Civil Registration System was established (Kyvik *et al*. 1996; Harvald *et al*. 2004).

### The linkage

Through record linkage between the Danish Twin Registry, the Danish Psychiatric Central Research Register and the Danish Civil Registration System, a cohort of 'High-Risk' twins was identified. This linkage identified same-sex twin pairs in which one twin had been treated in a psychiatric hospital setting for an affective episode (the proband) and the other twin had not been treated for affective disorder, the High-Risk healthy 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, 296.89, 296.99; ICD-10 codes F32–33.9) or a first diagnosis of manic mixed episode or bipolar affective disorder (ICD-8 codes 296.19, 296.39; ICD-10 codes F30–31.6, F34.0 F38.00). Control-twins (Low-Risk) were ascertained from twin pairs, where none of the co-twins had a known personal history of hospital contact with affective disorder, and matched on age, sex and zygosity for each High-Risk twin.

### Participants

Healthy monozygotic (MZ) and dizygotic (DZ) twins with and without a co-twin with a history of affective disorder were identified through nationwide registers. Accordingly, four groups were identified: (1) twins at high risk for development of affective disorder (MZ twin, co-twin affected), called High-Risk MZ twins; (2) twins at moderate high risk for development of affective disorder (DZ twin, co-twin affected), called High-Risk DZ twins; (3) twins at moderate low risk for development of affective disorder (DZ twin, co-twin unaffected), called Low-Risk DZ twins; and (4) twins at low risk for development of affective disorder (MZ twin, co-twin unaffected), called Low-Risk MZ twins.

In brief, 408 High-Risk and Low-Risk twins were invited and 271 agreed to participate. Subsequently, 37 individuals 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. In addition, a fifth group was defined as twins having a first-degree relative other than a twin with affective disorder or schizophrenia. This group ($n=18$) was excluded in the present analyses because they had a family history of mixed psychiatric disorders, but their co-twins were not affected. Finally,

10 participants were interviewed by telephone and three had impaired vision. Participants and non-participants have been described in detail elsewhere (Christensen *et al*. 2006).

## Ethics

The Danish Ministry of Health, The Danish Scientific Ethical Committee [(KF)-12-122/99 and (KF)-01-001/02] and the Danish Data Protection Agency approved the study. The study was conducted in accordance with the latest version of the Declaration of Helsinki. All participants gave written informed consent.

## Assessment

Participants were rated in a face-to-face interview using semi-structured interviews: diagnoses were made using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1 (Wing *et al*. 1990). All persons with a lifetime (current or past) diagnosis of affective disorder, schizo-affective disorder or schizophrenia according to the SCAN interview were excluded from the study. Participants with a lifetime minor psychiatric diagnosis defined as a non-organic, non-schizophrenic or non-affective SCAN diagnosis were included in the study. The 17-item Hamilton Depression Scale (HAMD; Hamilton, 1967) was used to assess depressive symptoms. Further self-rating of psychopathology was assessed using the Symptom Rating Scale for Depression and Anxiety, including assessment of depressive symptoms using the 21-item Beck Depression Inventory (BDI-21; Beck *et al*. 1961), manic symptoms using the six-item Mania Subscale (Beck *et al*. 1988) and anxiety symptoms using the 14-item Anxiety Subscale (BDI-14; Beck *et al*. 1988).

At the end of the interview, participants were interviewed about the lifetime family psychiatric history of first-degree relatives (their biological parents, co-twin, siblings and offspring) based on the Brief Screening for Family Psychiatric History questionnaire described by Weissman *et al*. (2000). They were asked specifically about depression, mania and schizophrenia among their first-degree relatives and questioned whether probands had been admitted to psychiatric hospital or received medical treatment for any psychiatric disorder.

The Cambridge Cognitive Examination (CAMCOG) was also used (Roth *et al*. 1986). CAMCOG is a detailed neuropsychological instrument incorporating a brief neuropsychological battery, especially sensitive to mild cognitive dysfunction; its ability to distinguish between demented, depressed and normal individuals has been approved (Hendrie *et al*. 1988). The test is capable of measuring the more general and diffuse nature of cognitive symptoms and 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. Thus, the test includes measures of language processing, working memory, episodic memory and declarative memory and the explicit recall of previously learned information. The maximum total score CAM COG-R is 105 (Roth & Huppert, 2002). The items measuring general knowledge (e.g. When did World War II start?) were not standardized for younger persons, so the six items (items 166–171) were omitted in the Cambridge Cognitive Examination – Revised (CAMCOR) score, resulting in a maximum total CAMCOR score of 99.

The Trail Making Test (Reitan, 1992) is a test of both selective and sustained attention. Participants were asked to connect printed numbered (1–25) circles on one worksheet in consecutive order, Trail A. In the second part, Trail B, they were asked to connect the numbers 1 to 13 and letters A to K (e.g. 1-A, A-2, 2-B, B-3) on a new worksheet. In the present study, the difference score between Trails A and B (Trail A-B) was examined as a measure of selective and sustained attention. All participants were given the same instructions and urged to work as fast as possible. Errors were corrected and the trails were timed, a high score indicating poor performance. A review of the neuropsychology of bipolar disorder found that six studies had compared the performance on the Trail Making Test of controls with that of remitted bipolar patients; the performance of the bipolar patients on the test was worse in all studies, although the differences did not all reach significance (Quraishi & Frangou, 2002).

The Stroop test is a test of frontal executive function and attention (Stroop, 1935; Golden & Freshwater, 2002). The Stroop stimuli involve, at a basic level, the ability of an individual to

Table 2. *Comparison of cognition performances according to unipolar risk status*

| | High-Risk MZ | High-Risk DZ | Low-Risk DZ | Low-Risk MZ | *p* |
|---|---|---|---|---|---|
| Number | 28 | 66 | 52 | 36 | |
| Age (yr) | 43·5 (14·4) | 47·5 (12·4) | 46·3 (12·4) | 38·3 (13·1) | 0·04 |
| Sex M/F | 11/17 | 25/44 | 12/31 | 11/15 | 0·79 |
| Education | 11·0 (2·9) | 11·9 (3·5) | 13·2 (2·9) | 14·2 (2·8) | 0·004 |
| Trail A | 38 (18) | 34 (12) | 29 (10) | 28 (10) | 0·001 |
| Trail A-B | 52 (25) | 46 (25 | 41 (20) | 33 (16) | 0·003 |
| Stroop | −3 (10) | −2 (9) | −1·0 (9) | 3 (10) | 0·007 |
| Colour-Word | 47 (12) | 50 (13) | 53 (11) | 57 (13) | 0·005 |
| CAMCOR | 91 (3) | 93 (3) | 95 (3) | 96 (2) | 0·0001 |

Values are number or mean (S.D.).
MZ, monozygotic; DZ, dizygotic; CAMCOR, Cambridge Cognitive Examination – Revised.

sort information from his or her environment and to selectively react to this information (Golden & Freshwater, 2002). The test consists of three pages. Each page has 100 items, presented in five columns of 20 items. The first page (Word, W) includes colour names, which have to be read as quickly as possible. The second page (Colour, C) includes colour patches (XXXX printed in red, blue or green), which have to be named. The third page (Colour-Word, CW) consists of colour names printed in incongruent colours (e.g. the word red is never printed in red ink). The colour of the ink has to be named, without paying attention to the word itself. Participants were given the same instructions and asked to read aloud for 60 seconds from each page and the number of words was recorded as the score. Analyses were made for the raw CW score and for Stroop, which is defined as the interference score [$W \times C/(W+C) = CW$ predicted and Stroop score = CW − CW predicted] and which is not dependent on the participant's reading or colour-naming speed (Golden & Freshwater, 2002). In cases where a person can inhibit the word-naming response, the CW score will be higher than predicted, yielding a positive value for the interference score, and visa versa.

### Statistical analyses

Univariate analysis and between-multiple-group comparisons were performed using analysis of variance (ANOVA) for three or more independent groups. The effect of the multiple variables age, sex and years of education on measures of cognition was analysed in multiple regression analyses with the cognition score (e.g. the Trail A score) as the dependent variable. The variables BDI-21 and BDI-14 were included as predictors because depressive and anxiety symptoms may influence cognition. The variable ICD-10 from the SCAN interview (a lifetime minor psychiatric diagnosis) was also included because minor psychiatric disorders may also influence cognitive function. The level of significance was set at 5% (two-tailed). All statistical analyses were undertaken with SPSS, version 13 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### The sample

The 203 participants were categorized into four groups according to their genetic liability for unipolar and bipolar disorders: 14 unipolar and seven bipolar High-Risk MZ twins, 69 unipolar and 14 bipolar High-Risk DZ twins, and 52 Low-Risk DZ twins and 36 Low-Risk MZ twins (see Tables 2 and 3). There were significant differences in age and years of education between unipolar risk groups (Table 2) and significant differences in age between bipolar risk groups (Table 3). No significant gender differences were found.

### Cognition and unipolar risk status

In Table 2, the 97 High-Risk twins with a unipolar co-twin were compared with the 88 Low-Risk twins. Univariate ANOVA showed significant group differences on all cognitive measures, with the High-Risk twins having the poorest cognitive performance. Thus, the High-Risk twins scored significantly higher on Trail A and Trail A-B and significantly lower on Stroop, CW and CAMCOR.

Table 3. *Comparison of cognition performances according to bipolar risk status*

| | High-Risk MZ | High-Risk DZ | Low-Risk DZ | Low-Risk MZ | *p* |
|---|---|---|---|---|---|
| Number | 7 | 14 | 52 | 36 | |
| Age (yr) | 40·6 (13·2) | 43·3 (12·3) | 46·3 (12·4) | 38·3 (13·1) | 0·04 |
| Sex M/F | 2/5 | 8/6 | 21/31 | 11/25 | 0·34 |
| Education | 12·5 (2·5) | 12·4 (3·3) | 13·2 (2·9) | 14·2 (2·8) | 0·17 |
| Trail A | 30 (8) | 28 (10) | 29 (10) | 28 (10) | 0·93 |
| Trail A-B | 46 (38) | 46 (25) | 41 (19) | 33 (16) | 0·10 |
| Stroop | 0 (8) | −5 (10) | −1·0 (9) | 3 (10) | 0·07 |
| Colour-Word | 52 (17) | 48 (12) | 53 (11) | 57 (13) | 0·12 |
| CAMCOR | 92 (4) | 93 (2) | 95 (3) | 96 (2) | 0·0001 |

Values are number or mean (S.D.).
MZ, monozygotic; DZ, dizygotic; CAMCOR, Cambridge Cognitive Examination – Revised.

In the multiple regression analyses, the association between unipolar risk status and cognitive scores was adjusted for differences in age, sex, years of education, scores on BDI-21 and BDI-14 and the prevalence of an ICD-10 minor psychiatric diagnosis. The associations between unipolar risk status and Trail A ($B=1{\cdot}38$, S.D. $=0{\cdot}57$, $p=0{\cdot}02$) and Trail A-B ($B=2{\cdot}32$, S.D. $=1{\cdot}04$, $p=0{\cdot}03$) were significant. The association between unipolar risk status and CW score was marginally significant ($B=-0{\cdot}96$, S.D. $=0{\cdot}56$, $p=0{\cdot}09$) and significantly associated with a lower CAMCOR score ($B=-0{\cdot}92$, S.D. $=0{\cdot}14$, $p=0{\cdot}0001$), but non-significantly with the Stroop score ($B=-0{\cdot}70$, S.D. $=0{\cdot}48$, $p=0{\cdot}14$). Age was significantly associated with Trail A ($B=0{\cdot}43$, S.D. $=0{\cdot}06$, $p=0{\cdot}0001$), Trail A-B ($B=0{\cdot}44$, S.D. $=0{\cdot}12$, $p=0{\cdot}0001$), CW ($B=-0{\cdot}32$, S.D. $=0{\cdot}06$, $p=0{\cdot}0001$) and Stroop ($B=-0{\cdot}26$, S.D. $=0{\cdot}05$, $p=0{\cdot}0001$). Number of years of education was significantly associated with CW ($B=1{\cdot}13$, S.D. $=0{\cdot}26$, $p=0{\cdot}0001$), Trail A-B ($B=-1{\cdot}93$, S.D. $=0{\cdot}50$, $p=0{\cdot}0001$) and CAMCOR ($B=0{\cdot}39$, S.D. $=0{\cdot}07$, $p=0{\cdot}0001$). There was no significant association between sex and any of the cognitive measures (data not shown).

## Cognition and bipolar risk status

In Table 3, the 21 High-Risk twins with a bipolar co-twin were compared with the 88 Low-Risk twins. Univariate ANOVA showed that the High-Risk twins scored significantly lower on CAMCOR and marginally significantly lower on the Stroop test.

In the multiple regression analyses, the association between bipolar risk status and cognitive scores was adjusted for the described variables. Bipolar risk status was not significantly associated with scores on Trail A ($B=-0{\cdot}36$, S.D. $=0{\cdot}72$, $p=0{\cdot}61$), Trail A-B ($B=2{\cdot}62$, S.D. $=0{\cdot}66$, $p=0{\cdot}09$), CW ($B=-1{\cdot}29$, S.D. $=0{\cdot}82$, $p=0{\cdot}12$) or Stroop ($B=-1{\cdot}14$, S.D. $=0{\cdot}69$, $p=0{\cdot}10$). Bipolar risk status contributed significantly to a lower CAMCOR score ($B=-0{\cdot}62$, S.D. $=0{\cdot}20$, $p=0{\cdot}002$). Age was significantly associated with Trail A ($B=0{\cdot}32$, S.D. $=0{\cdot}07$, $p=0{\cdot}0001$), Trail A-B ($B=0{\cdot}60$, S.D. $=0{\cdot}15$, $p=0{\cdot}0001$), CW ($B=-0{\cdot}40$, S.D. $=0{\cdot}08$, $p=0{\cdot}0001$) and Stroop ($B=-0{\cdot}30$, S.D. $=0{\cdot}07$, $p=0{\cdot}0001$). Number of years of education was significant associated with Trail A-B ($B=-1{\cdot}31$, S.D. $=0{\cdot}66$, $p=0{\cdot}05$), CW ($B=0{\cdot}77$, S.D. $=0{\cdot}35$, $p=0{\cdot}03$) and CAMCOR score ($B=0{\cdot}35$, S.D. $=0{\cdot}08$, $p=0{\cdot}0001$). Female sex was significantly associated with CW ($B=6{\cdot}4$, S.D. $=1{\cdot}93$, $p=0{\cdot}001$). Finally, BDI-14 was significantly associated with Trail A ($B=1{\cdot}23$, S.D. $=0{\cdot}72$, $p=0{\cdot}05$).

## Cognition scores according to unipolar and bipolar risk status and zygosity

In Table 4, participants were divided according to zygosity. Univariate analyses using the $\chi^2$ test for two independent samples showed that the MZ High-Risk twins with a unipolar co-twin had significant impairments on all cognitive measures compared to MZ Low-Risk twins. The MZ High-Risk twins with a bipolar co-twin had significant impairments only on the CAM COR score. Univariate analyses showed that the DZ High-Risk twins with a unipolar co-twin had significant impairments on Trail A and on CAMCOR compared to the DZ Low-Risk twins. The DZ High-Risk twins with a bipolar co-twin had significant impairments on the

Table 4. *Comparison of cognition scores according to unipolar and bipolar (indicated in bold) risk status and zygosity in twins*

| | High-Risk MZ | Low-Risk MZ | $\chi^2$ | High-Risk DZ | Low-Risk DZ | $\chi^2$ |
|---|---|---|---|---|---|---|
| *n* | 28<br>**7** | 36 | | 69<br>**14** | 52 | |
| Trail A | 38 (18)<br>**30 (8)** | 28 (10) | 0·01<br>**0·45** | 34 (12)<br>**28 (10)** | 29 (10) | 0·02<br>**0·62** |
| Trail A-B | 52 (25)<br>**46 (38)** | 33 (16) | 0·001<br>**0·82** | 46 (25)<br>**46 (25)** | 41 (20) | 0·16<br>**0·79** |
| Colour-Word | 47 (12)<br>**52 (17)** | 57 (13) | 0·002<br>**0·60** | 50 (13)<br>**48 (12)** | 53 (11) | 0·10<br>**0·16** |
| Stroop | −4 (11)<br>**0 (8)** | 3 (10) | 0·0001<br>**0·49** | −1 (9)<br>**−5 (10)** | −1 (8) | 0·51<br>**0·003** |
| CAMCOR | 91 (3)<br>**92 (4)** | 96 (2) | 0·03<br>**0·009** | 93 (2)<br>**95 (3)** | 95 (3) | 0·01<br>**0·19** |

Values are number or mean (S.D.).
MZ, monozygotic; DZ, dizygotic; CAMCOR, Cambridge Cognitive Examination – Revised.

Stroop score compared to the DZ Low-Risk twins.

## DISCUSSION

### Main results

Healthy twins with a co-twin with a history of unipolar disorder showed lower performance on all measures of cognitive function (selective and sustained attention, executive function, language processing and working and episodic memory) in univariate analyses and on almost all measures after adjusting for demographic variables, subclinical symptoms and minor psychopathology. Healthy twins with a co-twin with a history of bipolar disorder showed lower performance on tests measuring declarative and working memory, and also after adjustment for multiple variables. Cognitive impairment seems to be related to genetic liability, as the MZ High-Risk twins overall had the poorest performance on the cognitive scores (Table 1) and they had significant impairment on all measures of cognitive function, while the DZ High-Risk twins presented with significant lower scores on only Trail A and CAMCOR (Table 4). It was not possible to ascertain whether certain cognitive impairments, such as executive function, were specifically associated with unipolar or bipolar disorder because of the low number of High-Risk twins with a bipolar proband.

### Comparisons with other studies

The results of the present study regarding the High-Risk twins with a bipolar co-twin are in accordance with results from the six out of nine studies that found impairment in cognitive performance mainly on tasks concerning selective attention, inhibition and set shifting (Table 1), although it is problematic to compare studies across different cognitive measures. The results from one study that included MZ twins (Gourovitch *et al.* 1999) and are in accordance with those of the present study. The twin study from Finland (Kieseppa *et al.* 2005) found differences concerning only the female co-twins of bipolar twins, although the study mainly included DZ twins and the mean age (45·8 years) was above the average age of onset of bipolar disorder.

### Genetic liability

To our knowledge, this is the first study that has investigated cognitive function in relatives of individuals with unipolar disorder. These twins presented with a significantly poorer performance on more measures compared with the twins whose co-twins were affected by bipolar disorder. The differences between the unipolar and the bipolar High-Risk twins might be due to lack of power concerning the low number of twins with a bipolar co-twin. Twin studies of bipolar disorder have shown concordance rates of 0·36–0·80 for MZ twins and 0·04–0·19 for DZ twins (Bertelsen *et al.* 1977; Kendler *et al.* 1993; McGuffin *et al.* 2003; Kieseppa *et al.* 2004). A review of twin studies and unipolar disorder found concordance rates of 0·23–0·67 for MZ twins and 0·14–0·43 for DZ twins (Sullivan *et al.*

2000). Affective disorders are heterogeneous and 10% of patients with an index diagnosis of depression will subsequently develop a bipolar disorder (Akiskal *et al.* 1995) and there is a genetic overlap between unipolar and bipolar disorder (McGuffin *et al.* 2003). Findings from the present study suggest that cognitive dysfunction may be an unspecific marker for affective disorder in general.

How can these discrete cognitive impairments be explained? No studies have investigated the association between cognitive function in individuals at risk for either unipolar or bipolar disorder and brain imaging. Both executive dysfunction and slow information processing may act through frontostriatal disconnection and disruptions in white matter integrity would be expected to slow processing speed in all affected domains (Sheline *et al.* 2006). From the present finding of a lower processing speed in the High-Risk twins with a unipolar co-twin, a possible association between cognition and white matter changes may exist. Regarding bipolar disorder, a family study using magnetic resonance imaging (MRI) suggested that medial frontal and striatal grey matter deficits might be related to increased genetic liability to bipolar disorder (McDonald *et al.* 2004). However, a recent study found no relationship between genetic liability to affective disorder and either white or grey matter volume (McIntosh *et al.* 2006).

Another explanation for the discrete cognitive dysfunction might be an altered hypothalamic–pituitary–adrenal (HPA) axis physiology. Cortisol is a promising biological endophenotype for depression and abnormal cortisol responses in depressed patients and high-risk probands and controls have been found to be stable over time (Modell *et al.* 1998) and independent of depressive states (Zobel *et al.* 1999). Cortisol may influence the brain, resulting in impaired memory skills mediated through the hippocampus. In high-resolution MRI, depression has been associated with hippocampal atrophy ranging from 8% to 19% (Sheline *et al.* 2002).

A common genetic polymorphism in the brain-derived neurotrophic factor (BDNF) gene val66met has been shown to regulate the secretion of BDNF and also hippocampal function and episodic memory (Egan *et al.* 2003). In a large sample of normal individuals, it was found that this polymorphism seems to affect the anatomy of the hippocampus and prefrontal cortex, identifying a genetic mechanism of variation in brain morphology to learning and memory (Pezawas *et al.* 2004). To explain the cognitive changes found, healthy high-risk individuals need to be further investigated using brain imaging in combination with measures of genetic polymorphism that may influence brain morphology.

### Age/sex

In the present study, older age was associated with a poorer performance of both high- and low-risk twins in cognitive tests of processing speed, executive function, working and episodic memory. Higher education level was positively associated with cognitive function in accordance with the results of other studies (Sheline *et al.* 2006). The onset of bipolar disorder is most frequently reported in late adolescence and early adulthood (Pini *et al.* 2005), while the onset of unipolar disorder is most frequently reported in early adulthood and gradually up to 40–45 years (Hasin *et al.* 2005). Thus, if the High-Risk twins in the present study have passed the average age of onset, it is possible that the older High-Risk twins may present with a genetic resilience rather than a genetic risk.

Most clinical and epidemiological studies of depression have found higher prevalence rates among females with a gender sex ratio of 2 : 1 (Angst *et al.* 2002; Paykel *et al.* 2005) but almost equal rates in bipolar disorder (Pini *et al.* 2005). In the present study, concerning High-Risk twins with a bipolar co-twin, female sex was significantly associated with poor performance on the test of selective and sustained attention (Colour-Word) in accordance with the two twins studies referred to in Table 1. Sex differences in the response of the HPA axis to stress seem to be important and in studies of major depression, women have shown a greater responsiveness than men to stress (Young, 1998). Thus, future studies should consider investigating whether cognitive dysfunction is related to sex.

### Limitations

First, the High-Risk and Low-Risk twins were not matched on IQ. The results were analysed in a multiple regression model with years of

education as an adjusting variable, but this variable may not be a sufficient substitute for an IQ score. Second, the cognitive tests did not cover all cognitive functions. Third, in the present study, participants with a minor lifetime psychiatric diagnosis were included in both the High-Risk and the Low-Risk groups. None had received medical treatment and most had no actual problems. If persons with a lifetime minor psychiatric diagnosis are excluded, the probability of finding differences in cognitive performance and other variables between High-Risk and Low-Risk persons may be reduced (type II error). In our study, lifetime ICD-10 minor psychiatric diagnosis was included as a predictor in the multiple regression models. Four of the studies from Table 1 also included participants with minor psychiatric diagnoses (Gourovitch *et al.* 1999; Ferrier *et al.* 2004; Kieseppa *et al.* 2005; Clark *et al.* 2005*b*). Fourth, the probands' diagnoses are based on registry information from their first admission and their diagnoses might have changed.

### Strengths

The sample was population based, and using registers did not necessitate asking the proband for permission to contact the High-Risk twin. Asking for permission is the normal procedure in other High-Risk studies (Hirschfeld *et al.* 1989) and can create selection bias. The High-Risk and the Low-Risk groups were chosen using the same criteria, which reduced selection bias. The investigator (M.V.C.) was initially blinded for the risk status of the twins. Participants were not previously or at the time of investigation treated with psychopharmacological medicine, which is often a problem in studies on cognition in patients with affective disorder because of the possible cognitive side-effects of the medical treatment. None of the participants had an ongoing psychoactive substance abuse. By using register linkage and including twins discordant for unipolar disorder, it was possible to identify a considerably larger sample than in the family studies presented in Table 1. Finally, subclinical depressive and anxiety symptoms may be associated with a decline in cognitive function (Kessing, 1998; Butters *et al.* 2004), and in the present study analyses were adjusted for the effect of subclinical symptoms (score on BDI-14 and BDI-21). This was the case in only two of the studies included in Table 1 (Ferrier *et al.* 2004; Clark *et al.* 2005*b*).

## CONCLUSIONS

The findings of the present study indicate that healthy High-Risk twins seem to present with discrete cognitive abnormalities concerning language processing, declarative memory and executive function compared to healthy control twins. The cognitive abnormalities persisted after adjustment for subclinical psychopathology and the prevalence of a lifetime minor psychiatric diagnosis. The cognitive impairment was found to dependent on genetic liability. The results support the hypothesis that cognitive abnormalities may be present before the onset of unipolar and bipolar disorder and that cognitive performance might be a candidate endophenotype for mood disorder. Future twin studies and studies of probands with unipolar and bipolar disorder using a broad battery of neuropsychological measures in combination with neuroimaging and selected genetic polymorphism are recommended.

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## DECLARATION OF INTEREST

None.

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