Psychological Medicine, 1998, **28**, 1027–1038. Printed in the United Kingdom
© 1998 Cambridge University Press

Cognitive impairment in the euthymic phase of affective disorder

LARS VEDEL KESSING[1]

From the Department of Psychiatry, University of Copenhagen and Department of Psychiatric Demography, University of Aarhus, Denmark

ABSTRACT

Background. A review of studies of cognition in the euthymic phase of unipolar and bipolar affective disorder reveals diverging results.

Methods. The study was designed as a controlled cohort study, with the Danish psychiatric case register of admissions used to identify patients and the Danish civil register to identify controls. Patients who were hospitalized between 19 and 25 years ago with an affective diagnosis and who at interviews fulfilled criteria for a primary affective unipolar or bipolar disorder, according to ICD-10, were compared with age- and gender-matched controls. Interviews and assessment of the cognitive function were made in the euthymic phase of the disorder. In all, 118 unipolar patients, 28 bipolar patients and 58 controls were included. Analyses were adjusted for differences in the level of education and for subclinical depressive and anxiety symptoms.

Results. Patients with recurrent episodes were significantly more impaired than patients with a single episode and more impaired than controls. Also, within patients the number of prior episodes seemed to be associated with cognitive outcome. There was no difference in the severity of the dysfunction between unipolar and bipolar patients.

Conclusions. Cognitive impairment in out-patients with unipolar and bipolar disorder appears to be associated with the number of affective episodes.

INTRODUCTION

A majority of studies have found memory impairment in depressed patients (for a meta-analysis of studies see Burt *et al*. 1995) but only a few studies have investigated cognition in the euthymic phase of affective disorder. A review of such studies reveals diverging results, although most studies find cognitive dysfunction in one or more neuropsychological tasks (see Table 1). Possible explanations for the divergent results may be found in various factors in the studies.

Selection bias

Strong selection bias occurred in the majority, if not in all, of the studies. As can be seen from Table 1, the patient samples were in general small, and since cognitive impairment presumably only exists in a subset of patients with affective disorder (Burt *et al*. 1995; King & Caine, 1996) the results of a study with a small sample size will be crucially affected by the composition of the patients included. Similarly, the control groups were small (Table 1), often gathered from high school students or hospital staff, contacted unsystematically or via advertising and often by offers of payment, all of which implies possibilities of selection bias and potential confounding (Hennekens & Buring, 1987, pp. 137–142). In two studies (Fromm & Schopflocher, 1983; Tham *et al*. 1997), the control group was taken from a database of normal controls whereas in four studies, no information was provided about the origin of the control group (Sapin *et al*. 1987; Coffman *et al*. 1990; Bulbena & Berrios, 1993; Trichard *et al*. 1995).

Some studies did not match or adjust for

[1] Address for correspondence: Dr Lars Vedel Kessing, Department of Psychiatry, Rigshospitalet, Blegdamsvej 9, DK 2100 Copenhagen Ø, Denmark.

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

Table 1. *Cross-sectional and short-term studies of cognitive function in euthymic state of affective disorder*

Reference	Year	*N* Patients/Controls	Mean age of mood patients	Cognitive dysfunction in affective disorder
Unipolar patients				
Fromm & Schlopflocher	1984	29/142 + 31 neurotics	43	No difference between the three groups in an expanded Halstead–Reitan battery
Coello *et al.*	1990	23/20	15	Visual spatial tasks
Abas *et al.*	1990	20/20	70	Visuospatial memory and learning
Marcos *et al.*	1994	28/19	54	Immediate visual memory, delayed logical and visual memory, paired learning, block design
Trichard *et al.*	1995	19/14	47	Stroop Color Word Test No diff. in Verbal Fluency Test
Beats *et al.*	1996	19/15	74	Response latency and in spatial recognition No diff. in tests of working and visuospatial memory
Bipolar patients				
Calev *et al.*	1986	10/10	35	No difference in verbal and non-verbal recall
Sapin *et al.*	1987	20/20	37	Masked face recognition task Street Gestalt Completion Test
Morice	1990	20/34 + 60 schizo.	45	Wisconsin Card Sorting Test (No difference between bipolar and schizoph.)
Coffman *et al.*	1990	30/52	33	Verbal and non-verbal tasks, bilateral sensory and motor tasks, Wisconsin Card Sorting Test
Mixed unipolar and bipolar patients				
Savard *et al.*	1980	16 (6 unip.)/42	37	Halstead–Reitan categories test
Johnstone *et al.*	1985	29 (4 unip.)/510 schizo.	68	Withers & Hinton test battery (No difference between affect. and schizoph.)
Bulbena & Berrios	1993	33/30	50	Benton Lines test No difference in: attention, memory, visuospatial function and choice reaction time
McKay *et al.*	1995	24 (22 unip.) 11 (10 unip.) 10 (1 unip.) chronic/severe	45 78 64	None impaired in memory executive or intellectual function, 5 impaired on at least one measure
Harvey *et al.*	1997	50/308 schizo (chronically hospitalized)	75	No overall difference between affect. and schizoph. in: Boston Naming Test; Praxic drawing test; and Word list learning and recall
Tham *et al.*	1997	10 unip., 16 bip./400	26	Synonym reasoning and block-test battery: part of Halstead–Reitan test battery

differences in the level of education or premorbid intelligence between the patient and the control group (Fromm & Schopflocher, 1983; Coffman *et al.* 1990; Bulbena & Berrios, 1993). No study provided information on the number of non-participants among patients and among controls (i.e. subjects who were asked but refused to participate in the study), their socio-demographic data or characteristics of the illness, which makes it impossible to estimate the degree of selection bias and thus the generalizability of the studies.

Subclinical psychopathology

Only a few studies presented measures of the extent of subclinical depressive symptoms at the time of investigation of the patients (Fromm & Schopflocher, 1983; Abas *et al.* 1990; McKay *et al.* 1995; Trichard *et al.* 1995; Beats *et al.* 1996). Similarly, no study of bipolar patients demon-

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

strated measures of the extent of manic symptoms. Often the patients are simply described as euthymic, recovered or just ambulatory out-patients. In particular, no study adjusted for subclinical depressive or manic symptoms in a multiple regression model. The importance of this pitfall, of not paying attention to subclinical psychopathology, is emphasized by Abas *et al*. (1990), who found that the quantitatively low MADRS score of depression in recovered patients correlated significantly with the neuropsychological deficits, and also by a study of a community-based sample, which showed that the level of self-reported subclinical depression partly predicted the cognitive performance (La Rue *et al*. 1995). Similarly, although the level of anxiety may affect cognitive function, only one study investigated this correlation (Trichard *et al*. 1995).

Psychoactive treatment

Although most studies mention the current psychoactive treatment, no study paid attention to previous treatment and few to the history of ECT (Abas *et al*. 1990; Marcos *et al*. 1994; Harvey *et al*. 1997).

Cognitive tests

Finally, the studies used discrete and specialized psychological tasks or tests with the aim of measuring localized cognitive dysfunction (see Table 1) and thereby ignored the general and diffuse nature of cognitive impairment in affective disorder (Poon, 1992; Tarbuck & Paykel, 1995; Robbins *et al*. 1996).

In conclusion, the diverging results can be explained by the inclusion of small selected samples of patients and controls, lack of correction of various degrees of subclinical psychopathology and the use of over-specialized tests.

The aim of the present study was to design a controlled cohort study which took account of most of the mentioned pitfalls and which included larger, more representative and systematically selected samples of patients and controls and access to information about non-participants. The Danish psychiatric case register of admissions was used to identify patients and the Danish civil register (Folkeregisteret) was used to identify controls.

METHOD

The registers

All inhabitants in Denmark have a unique person identification number that is used in all public registration systems and that can be logically checked for errors, so it can be established with great certainty if a person has been hospitalized, irrespective of changes in name, etc. All psychiatric admissions are registered in a nationwide register (Dupont, 1983; Munk-Jørgensen *et al*. 1993) with the same diagnostic system, the International Classification of Diseases, 8th Revision (National Board of Health, Denmark, 1971), from 1 April 1970 to 31 December 1993. Since there are no private psychiatric hospitals or clinics in Denmark, all admissions for the 5·1 million inhabitants are included in the register. The civil register contains current information about each citizen in Denmark (Ministry of the Interior, 1995).

The samples

The patient sample was identified via the Danish psychiatric case register as hospitalized patients with a manic-depressive main diagnosis (ICD-8 296), depressive or manic/circular episode, at a first discharge between 1971 and 1977, that will say at least 19 years ago, and who today were 40 years or older and lived in the municipality or county of Copenhagen (Københavns kommune eller amt). Two groups were selected: patients with one psychiatric admission and patients with three or more psychiatric admissions. Furthermore, to be included, patients had to fulfil criteria for an affective disorder according to ICD-10 (F30-F39, WHO, 1992), at an interview.

The control sample was identified via the civil register as persons living in a part of the municipality of Copenhagen (Østerbro) with access to the same kind of treatment facilities as the patient group. The controls were matched pair-wise by age and gender with the patients.

Exclusion criteria were: an auxiliary diagnosis of dementia (inclusive Alzheimer's dementia) or possible dementia at first admission or suspicion of any kind of persisting cognitive impairment at first admission according to the casenotes; significant physical (including neurological) illness; history of stroke; history of head trauma

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

leading to hospitalization; history of drug or alcohol abuse; ECT within the last 6 months or psychiatric admission within the last 3 months. Subjects with a score >8 on the Hamilton Depression Scale, 17 items (HDS; Hamilton, 1960) were re-contacted at suitable intervals and re-assessed several times, and if still depressive, these subjects were excluded.

Furthermore, patients who were diagnosed with other severe psychiatric disorder than affective disorder, according to ICD-10 (WHO, 1992), were excluded and controls who had a history of psychiatric admission or treatment or who were diagnosed with a major psychiatric disorder were excluded.

Assessment

Current diagnosis was computed according to ICD-10 (WHO, 1992) and the severity of depressive symptoms was assessed clinically with the Hamilton Depression Scale, 17 items (HDS; Hamilton, 1960). The cognitive function was assessed with five different measures. The Cambridge Cognitive Examination is a detailed neuropsychological instrument especially sensitive to mild cognitive dysfunction (CAMCOG; Roth *et al*. 1986; Huppert *et al*. 1995). Its ability to distinguish between demented, depressed and normal subjects has been found to be good (Hendrie *et al*. 1988). The Mattis Dementia Rating Scale is constructed to be sensitive to focal and diffuse brain damage (MDRS; Mattis, 1976). Both tests examine a wide range of areas within cognition, including orientation, language, attention, abstract thinking, verbal and non-verbal short-term and long-term memory, calculation, perception and praxis. The Gottfries-Bråne-Steen (GBS) Dementia Rating Scale is a shorter test but includes besides general cognitive functions also functions of daily life activity and emotion (GBS; Gottfries *et al*. 1982). The Mini-Mental State Examination (MMSE; Folstein *et al*. 1975) and the Global Deterioration Scale (GDS; Reisberg *et al*. 1988) were included as overall measures of cognition. Hachinski Ischaemic Score was used to exclude dementia of the vascular type (Hachinski *et al*. 1975). Self-rating of psychopathology was assessed with the Symptom Rating Scale for Depression and Anxiety (Bech, 1988) including assessment of depressive symptoms by the 21-item Beck Depression Inventory (BDI; Beck *et al*. 1961), manic symptoms by the 6-item Mania Subscale (Bech, 1988) and anxiety symptoms by the 14-item Anxiety Subscale (Bech, 1988).

The interviews were often carried out in the home of the participants, and if possible supplemented with information from family or carers. The interviews lasted 2 to 3 hours and were made by a psychiatrist who was trained in the use of the scales (L. V. K.). With the intention of making the interviewer blind to the status of the participants, the cognitive function was assessed before information about psychiatric history and treatment was elicited, but it was not always possible to prevent the participants from spontaneously talking about their psychiatric history.

For all patients, information about their previous course of illness was carefully extracted from their casenotes. If a patient had been treated by a general practitioner or by a private psychiatrist, detailed information was requested with the consent of the patient. Information about consumption of psychoactive drugs was gathered from the casenotes and supplemented with information from the patients, family members, doctors and professional carers.

All participants underwent a physical examination and a battery of laboratory tests: haemoglobin, leucocytes, thrombocytes, creatinine, potassium, sodium, blood-calcium, blood-glucose, erythrocyte sedimentation rate, aspartate-aminotransferase, alkaline phosphatase, bilirubin, T3, T4, cobalamine, erythrocyte-folate. Subjects who did not want to participate in a regular interview were asked to participate in a 5 min telephone interview about the number of affective episodes and the treatment since the latest report in their casenotes and about cognitive function and complaints according to the GDS.

Statistical analyses

Categorical data were treated with ordinary chi-square tests, data on interval scales were analysed with Mann–Whitney U test and continuous data with Student's t test for two independent groups. Correlations between measures of cognition were analysed with Pearson's correlation. The effect of multiple variables on measures of cognition was analysed in multiple regression analysis. To compare the effect of variables on cognition in unipolar and bipolar disorder, all variables were transformed

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

into new type-dependent variables. Subsequently, it was investigated if there was any interaction-effect between the type of illness and the variable, using the likelihood-ratio test. Throughout the study $P < 0{\cdot}05$ was used to indicate statistical significance.

RESULTS

In all, 273 patients were identified via the register and were alive with an address in the municipality or county of Copenhagen. Subsequently, 58 patients were excluded according to the mentioned criteria. Among the 215 remaining patients, 146 patients (67·9%) were included and interviewed; 118 patients had unipolar and 28 patients had bipolar disorder. All of the bipolar patients had had more than one episode of mood disturbances whereas 50 of the unipolar patients had had only one episode. Among the 69 patients who did not want to participate in the interview (the non-participants) 39 patients were interviewed by telephone.

Among 139 invited control persons, 16 were excluded according to the mentioned criteria. In all, 58 persons (47·2%) were interviewed, 65 did not want to participate (the non-participants) but 46 of these participated in the telephone interview.

Participants compared with non-participants

There were no significant differences in gender (female proportion: 67%–76%) or in current age (66 ± 14 years to 69 ± 13 years) between participants and non-participants within patients and within controls. Participants, whether patients or controls, were significantly more cognitively impaired according to GDS, than the telephone-interviewed non-participants (patients – GDS for participants $= 2{\cdot}1 \pm 1{\cdot}2$ *versus* GDS for non-participants $= 1{\cdot}6 \pm 0{\cdot}9$, $P < 0{\cdot}01$; controls – GDS for participants $= 1{\cdot}6 \pm 0{\cdot}8$ *versus* GDS for non-participants $= 1{\cdot}3 \pm 0{\cdot}6$, $P < 0{\cdot}05$). It was not possible to obtain information about the cognitive function for 30 patients (14% of the included patient sample) and for 19 controls (16% of the included control sample). However, none of these individuals lived in an institution.

Further analyses of the patient group revealed no significant differences between patients who participated in the study and patients who did not participate with regard to the distribution of unipolar *versus* bipolar patients, age at first admission, or the number of admissions. In contrast, participants, compared with the telephone-interviewed non-participants, had suffered significantly more episodes of mood

Table 2. *Sociodemographic variables and characteristics of the illness* (*mean* (*S.D.*))

	Unipolar ($N = 68$)	Bipolar ($N = 28$)	One episode ($N = 50$)	Control ($N = 58$)
Female gender (%)	69·1	57·1	70·0	63·8
Age	69·3 (12·7)	58·5 (14·2)*	66·3 (15·1)	66·1 (14·0)
Years of education	10·9 (3·8)	11·8 (3·5)	10·8 (3·8)	11·7 (4·0)
Hamilton	2·7 (2·7)**	1·8 (2·3)	1·4 (1·6)	1·1 (1·4)
Age at first affect. episode	42·1 (15·7)	32·6 (13·7)**		
Age at first treated episode	46·2 (13·6)	35·5 (14·1)**		
Age at first hospitalization	47·0 (13·1)	37·3 (13·5)**		
Age at last episode	62·0 (14·3)	51·4 (15·6)**		
Number of episodes	5·2 (3·7)	8·5 (6·9)**		
Number of depressions	5·2 (3·7)	3·3 (3·7)**		
Number of manias	—	5·2 (4·8)		
Number of hospitalizations	3·5 (2·2)	5·7 (5·0)*		
Duration of illness (years)	23·7 (4·5)	22·7 (4·6)		
Period since last affect. episode				
Totally (years)	7·8 (7·3)	7·6 (7·4)		
With prophylactic medicine	3·8 (5·8)	4·9 (6·1)		
Without prophylactic medicine	4·0 (7·0)	2·7 (2·5)		

* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$.

Gender, age and years of education, Hamilton: item compared with the corresponding item for controls. Other variables: item compared for recurrent unipolar and bipolar disorder.

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

Table 3. *Previous treatment with psychoactive drugs and ECT*

	N (%)	Time in years median (25%–75%)	1000 DDD median (25%–75%)
Lithium	49 (33·6)	8·9 (1·0–17·5)	3·5 (0·5–6·1)
Tricyclics	106 (72·6)	2·1 (0·6–6·0)	0·9 (0·3–2·7)
Neuroleptics	35 (24·0)	0·9 (0·1–6·5)	0·3 (0·1–0·9)
Benzodiazepines	55 (37·6)	5·1 (2·0–16·0)	1·8 (0·5–4·4)
ECT		number (25%–75%)	duration (s) (25%–75%)
Total	75 (51·4)	14 (9–25)	450 (313–780)
Unilateral	70 (47·9)	11 (9–17)	
Bilateral	33 (22·6)	8 (5–17)	

DDD: defined daily doses.
ECT: number = median number of ECTs given;
duration = median duration of convulsions measured in seconds.

swings (mean number of episodes participants non-participants, 4·4/2·7; $U = 2209{\cdot}5$; $P = 0{\cdot}03$).

Characteristics of the illnesses

As can be seen from Table 2, bipolar patients were on average younger at the onset of the illness and at the time of the investigation than unipolar patients with recurrent episodes and they had significantly more episodes and hospitalizations, but the duration of the illnesses from first-treated episode to the time of the investigation was approximately the same for the two disorders.

Current and previous treatment among participants

Previously given psychoactive treatment and electroconvulsive therapy (ECT) are described in Table 3. Psychoactive treatment is presented as the duration in years and as the number of defined daily doses (DDD) and ECT is presented as the number of ECTs given and the duration of the convulsions (visually or according to EEG monitoring). At the time of the study, 23 patients were in treatment with antidepressants, 29 with lithium, 21 with SSRI, 41 with benzodiazepines, 21 with neuroleptics, five with isocarboxacid, four with carbamazepin, whereas 62 patients took no psychoactive drugs at all. The patients had been stable for several years without affective episodes at the time of the study (Table 2).

Among the controls, 36 had previously been treated and six were currently being treated with hypnotics whereas none had been or were in treatment with anxiolytics or other kind of psychopharmaceutical. With regard to other types of medicine, a few patients and controls were treated with diuretics or non-narcotic analgesics in small doses, but most were not being treated currently with any somatic medicine.

Correlations between measures of cognition

MATTIS was the measure that had the lowest correlation with other measures (Pearsons correlation coefficient $|0{\cdot}59| < r < |0{\cdot}74|$; $P < 0{\cdot}001$) with the lowest correlation between MATTIS and MMSE ($r = |0{\cdot}59|$; $P < 0{\cdot}001$). All other measures had a high degree of correlation with each other ($|0{\cdot}75| < r < |0{\cdot}96|$; $P < 0{\cdot}001$). CAMCOG was the measure that correlated best with other measures with the highest correlation between CAMCOG and MMSE ($r = |0{\cdot}96|$; $P < 0{\cdot}001$).

Patients compared with controls

The patient group was divided into three groups: unipolar patients with more than one episode; bipolar patients (all of whom had more than one episode); and, patients with only one episode.

1 *Sociodemographic variables*

Among participants, bipolar patients were significantly younger than controls ($t = -2{\cdot}35$, $\mathrm{df} = 84$, $P = 0{\cdot}02$). There were no other significant differences in gender, age or level of education between any group of patients and controls (Table 2).

2 *Level of depressive and anxiety symptoms*

In univariate analysis, unipolar and bipolar patients with more than one episode scored

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

Table 4. *Scores on measures of cognition for patients with recurrent episodes and patients with a single episode compared with controls*

	> 1 Episode		1 Episode		Control	
Measure	Mean	(S.D.)	Mean	(S.D.)	Mean	(S.D.)
CAMCOG	99·9**	(23·8)	108·7	(10·9)	109·4	(8·6)
MATTIS	137·0*	(8·8)	139·1	(10·1)	139·5	(6·9)
MMSE	26·2**	(6·0)	28·4	(2·6)	28·5	(2·1)
GBS	11·5***	(20·4)	3·9	(5·3)	2·7	(3·8)
GDS	2·4***	(1·3)	1·7	(0·9)	1·6	(0·8)

* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$.

significantly higher than controls on the BDI-21 (mean unipolar, 10·7; mean bipolar, 7·9; mean controls 5·3, $P < 0{\cdot}05$) and unipolar patients also scored higher than controls on the BDI Anxiety Subscale (mean unipolar, 7·3; mean controls, 3·4; $U = 666{\cdot}0$; $P = 0{\cdot}001$). Patients with one episode did not differ significantly from controls either on the BDI-21 or on the BDI Anxiety Subscale (mean BDI-21, 5·3; mean Anxiety, 4·2).

3 *Cognitive function*

In univariate analysis, measures of BDI-21 correlated significantly with measures of MMSE ($r = -0{\cdot}16$; $P = 0{\cdot}05$), GBS ($r = 0{\cdot}43$; $P < 0{\cdot}001$) and GDS ($r = 0{\cdot}21$; $P = 0{\cdot}01$) but not with CAMCOG ($r = -0{\cdot}13$; $P = 0{\cdot}1$) and MATTIS ($r = -0{\cdot}07$; $P = 0{\cdot}4$). Additionally, measures of BDI Anxiety Subscale correlated with all five cognitive measures (r between 0·12 and 0·45; $P < 0{\cdot}05$) except the MATTIS measure ($r = -0{\cdot}13$; $P = 0{\cdot}2$).

The number of depressive episodes, the number of manic episodes and the total number of episodes did not predict scores on BDI-21 ($P > 0{\cdot}2$). Difference in cognitive function between unipolar and bipolar patients with recurrent episodes was found with MATTIS ($U = 417.5$; $P = 0{\cdot}02$) and with GDS ($U = 720$; $P = 0{\cdot}05$) in univariate analyses, but not with the other measures. In multiple regression analysis, adjusted for differences in gender, age, years of education and depressive and anxiety symptoms, there were no significant differences between unipolar and bipolar patients with recurrent episodes in any measure of cognitive function (results not presented). Using the likelihood-ratio test, the effect of the number of episodes and the duration of illness and the effect of all treatment variables on any of the five measures of cognition did not differ significantly for unipolar and bipolar patients (results not presented). The samples of unipolar and bipolar patients were consequently considered together and a common effect of the variables were estimated for the two disorders.

Patients with one episode did not differ in cognitive function from controls in any measure, whereas patients with more than one episode were significantly more impaired in all measures according to univariate analyses (Table 4). Furthermore, adjustment of differences in gender, age, years of education and depressive and anxiety symptoms in multiple regression analyses did not change this result (Table 5).

Among patients with recurrent episodes, 14·3% of bipolar patients and 16·2% of unipolar patients had a score on MMSE below 24 which is the cut-off for dementia (Folstein *et al.* 1975). In contrast, only 4·0% of patients with a single episode and 3·4% of controls scored in the demented range of MMSE.

Cognitive function within patients

1 *Characteristics of the illness and cognitive function*

In univariate analyses, patients with recurrent episodes were significantly more impaired than patients with one episode in all measures of cognition (results not presented). As can be seen from Table 6, the number of episodes was

Table 5. *Cognitive function for patients with recurrent episodes and for patients with a single episode compared with cognitive function for controls and adjusted for differences in gender, age, years of education and depressive and anxiety symptoms*

B (95% CI)	> 1 Episode	1 Episode
CAMCOG	−3·3 (−5·6 to −1·0)**	1·2 (−0·9 to 3·3)
MATTIS	−2·5 (−4·2 to −0·8)**	1·1 (−0·3 to 2·5)
MMSE	−0·7 (−1·4 to 0·0)*	0·4 (−0·2 to 1·7)
GBS	1·7 (0·2 to 3·2)*	0·3 (−1·1 to 1·8)
GDS	0·4 (0·1 to 0·7)**	0·0 (−0·8 to 1·7)

B: regression coefficient in multiple regression models.
* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$.

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

Table 6. *The effect of the number of total episodes, the number of depressive episodes and the number of manic episodes in affective disorder, adjusted for differences in gender, age, years of education, depressive and anxiety symptoms and the duration of the illness*

B (95% CI)	Total episodes	Depressive episodes	Manic episodes
CAMCOG	−0·2 (−0·5 to 0·0)*	−0·4 (−0·7 to −0·1)*	−0·1 (−0·5 to 0·4)
MATTIS	−0·2 (−0·4 to −0·1)**	−0·4 (−0·6 to −0·1)**	−0·2 (−0·5 to 0·1)
MMSE	−0·1 (−0·1 to 0·0)	−0·1 (−0·2 to 0·0)*	0·0 (−0·1 to 0·1)
GBS	0·1 (−0·1 to −0·2)	0·2 (0·0 to 0·4)	0·0 (−0·3 to 0·3)
GDS	0·0 (0·0 to 0·0)	0·0 (0·0 to 0·1)	0·0 (−0·1 to 0·0)

B indicates the regression coefficient in multiple regression models for one affective episode.
* $P < 0·05$; ** $P < 0·01$.

significantly associated with cognitive decline measured with CAMCOG and MATTIS, when adjusted for gender, age, years of education, depressive and anxiety symptoms and the duration of the illness, but there was no significant association with the three other measures of cognition. The value of CAMCOG and of MATTIS declined 0·2 units for each new affective episode (95% CI, 0·5–0·0 and 0·4–0·1 respectively). Further analyses revealed that it was the number of depressive episodes that correlated with cognitive decline whereas the number of manic or mixed episodes had no significant effect on any of the five measures (Table 5). The duration of the illness had no significant effect on any of the measures ($B <$ 0·05 per year of illness; $0·33 < P < 0·98$).

2 *Treatment and cognitive function*

The number of DDD of lithium was the only previous treatment that affected cognition. For every 1000 DDD the value of CAMCOG decreased 0·7 unit (95% CI, 0·2–1·1; $P < 0·01$) and the value of MATTIS 0·4 unit (95% CI, 0–0·8; $P < 0·05$). The same results were found in analyses where previous treatment was included as the duration of treatment (lithium: CAMCOG, $B = -0·3$ (95% CI, −0·5 to 0), $P < 0·05$; MATTIS, $B = -0·2$ (95% CI, −0·4 to 0), $P < 0·05$). The number of ECTs had no significant effect, neither had the number of unilateral or the number of bilateral treatments nor the duration of convulsions ($B < 0·5$; $P >$ 0·05). Patients in current psychoactive treatment of any kind had a significantly lower score on the MATTIS scale than patients not in psychoactive treatment (−2·3 (95% CI, −4·4 to −0·2) $P < 0·05$) but current psychoactive treatment did not affect any other scale.

3 *Characteristics of the illness, treatment and cognitive function*

All analyses were repeated with inclusion of sex, age, years of education, current depressive and anxiety symptoms, previous and current treatment and the duration of the illness and the number of episodes and followed by backward stepwise removal of variables. Apart from age and years of education, the number of episodes was the only variable that contributed significantly to decline in measures of CAMCOG ($B = -0·7$ (95% CI, 1·3 to −0·1), $P = 0·03$) and GBS ($B = 0·6$ (95% CI, 0·1–1·2), $P = 0·03$). The number of ECTs correlated with GDS ($B = 0·2$ (95%, 0–0·3), $P = 0·004$) but not with any other measure. No other significant correlations were found between the measures and the variables included.

In conclusion, the most consistent significant finding in analyses within patients was the correlation between the number of episodes and cognitive decline as measured with CAMCOG. The number of episodes also correlated significantly in several analyses with MATTIS. Furthermore, lithium treatment correlated with cognitive impairment as indicated by CAMCOG and MATTIS.

DISCUSSION

Methodological aspects

Generalizability

Patients

The study is a follow-up of all patients with primary affective disorder and a first admission

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

for depression, mania or a circular episode more than 19 years ago and with no further psychiatric admissions or with two or more further admissions. The results are thus restricted to patients with at least one affective episode severe enough to lead to hospitalization and so cannot be generalized to apply to patients with mild affective disorder.

Participating patients had the same age and gender distribution but had more episodes and were more cognitively impaired than non-participating patients according to telephone interview. Not surprisingly, patients with fewer episodes were less willing to participate, but these patients were also less cognitively impaired than participating patients. Thus, the correlation between the number of episodes and cognitive function was the same in participating and non-participating patients.

Controls

It is well-known that individuals in the community are less motivated to participate in research projects than hospitalized controls (Hennekens & Buring, 1987, p. 140). The investigation was conducted from the National Hospital of Copenhagen, Rigshospitalet, and in the hope of benefiting from local people's sympathy with the hospital and the research, the control group was selected from people in the catchment area of Rigshospitalet. Nevertheless, the proportion of controls who agreed to participate was still low (47%). Participating controls had the same age and gender distribution as non-participating controls but were on average more cognitively impaired. In summary, participants seemed more cognitively impaired than non-participants but there is no reason to believe that the proportion of cognitively impaired subjects who were willing to participate was greater among patients than among controls. Thus, it seems reasonable to conclude that the samples of patients and controls included in the study are representative samples of patients with moderate to severe affective disorder and of gender- and age-matched controls in general.

The number of episodes

The number of affective episodes was estimated with the use of the life chart method (Roy-Byrne *et al*. 1985; Post *et al*. 1988). It is a major drawback in the study that the number of episodes was counted retrospectively. Patients, family members, carers and doctors might have forgotten moderate episodes and perhaps even severe episodes. Nevertheless, this drawback tends to work against a correlation between the number of episodes and cognitive impairment since the most impaired patients presumably might forget the most episodes. Furthermore, Roy-Byrne *et al*. (1985) found that the life chart method resulted in a high degree of reliability between measures of the illness estimated in a retrospective study and measures estimated in a subsequent prospective study.

Another problem that might affect the number of counted episodes, in every study of cognition in affective disorder, is the overlap between demential symptoms and depression. In the present study, episodes in patients with dementia were only counted as affective episodes if treatment resulted in significant improvement of daily life activities.

In summary, with the life chart method used, a conservative estimate of the number of episodes was provided.

Subclinical psychopathology

The study, together with other studies (Abas *et al*. 1990; La Rue & Carmelli, 1995), emphasizes the importance of adjusting for subclinical psychopathology in studies of the euthymic phase in affective disorder. Although patients indicated that they had been well for several years and at the interview scored < 9 on the HDS (17 items), patients with more than one episode scored significantly higher on a self-rating scale of depression and on a scale of anxiety than controls, and the degree of psychopathology correlated with some measures of cognition in univariate analyses.

Implications

Patients with recurrent affective disorder in the euthymic phase presented with cognitive impairment compared with patients with a single affective episode and compared with controls without affective disorder. This result seems reliable since the relation was consistently found across five different measures of cognition in univariate analyses and furthermore in analyses

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

with adjustment of differences in age, gender, years of education and subclinical psychopathology of anxiety and depression. No other study has analysed cognitive function separately for patients with recurrent affective disorder and for patients with a single episode. The difference in cognitive function between these two group of patients is one more reason for the discrepancies between previous studies since the proportion of patients with a single episode varies across the studies.

Further analyses of the total sample of patients, in the present study, revealed that the severity of cognitive impairment seemed to be associated with the number of episodes even after adjustment of previous psychoactive treatment. This relationship was, however, only found with two measures of cognition out of five and in analyses that included a great number of variables thus increasing the possibility of statistical significance by chance alone.

Nevertheless, the association was consistently found in several multiple regression analyses and taken together with the results from the previous analyses comparing patients with a single episode and patients with recurrent episodes, it appears that this finding is not due to chance.

It is emphasized that the number of episodes did not predict the severity of subclinical depressive symptoms according to self-rating with BDI-21 in the euthymic phase. So it did not appear to be the severity of episodes but the number of episodes *per se* that was associated with cognitive impairment. Furthermore, it is emphasized that no patients in the study presented with persisting cognitive dysfunction or were suspected for having any kind of dementia illness, inclusive Alzheimer's disease, at first admission according to the casenotes. It was, in every case, confirmed by relatives or others that the dysfunction had developed after the onset of illness. The observed cognitive impairment had thus in every case developed during the course of the affective disorder.

Treatment with lithium seemed to be related, in some degree, with cognitive dysfunction as in some other studies (Lund *et al*. 1982; Shaw *et al*. 1987). It is of course not possible to answer the question of causality from the present study and it is not possible to tell if the impairment was caused by the illness itself or by treatment. Nevertheless, analyses of the data suggested both possibilities, although the number of episodes seemed to be the most consistent predictor. No other study of cognition in the euthymic phase has, until now, included measures of the clinical history of the illness with measures of treatment.

It should be noted that the mean age of unipolar patients in the present study was > 65 years and it is possible that an association between the number of episodes and cognitive outcome may not be valid for younger patients. Nevertheless, the degree of cognitive impairment after recovery has been found to be similar for older and younger patients (Tarbuck & Paykel, 1995). The present study confirmed findings from our prior study in which cognitive impairment in old unipolar patients correlated with the number of psychiatric admissions and the number of episodes and less with the duration of the illness (Kessing *et al*. 1996). As in the present study, current or previous treatment or differences in social characteristics could not explain the dysfunction. The results are further in accordance with findings in a study of 26 euthymic patients with recurrent affective disorder among which patients with impaired cognitive functioning had more hospitalization episodes than patients with normal cognitive functioning (Tham *et al*. 1997).

Few studies have investigated other associations with recurrence in affective disorder. However, the number of prior depressive episodes has been found to correlate with response latencies in test performance (Beats *et al*. 1996). It is well known that bipolar patients on average have more episodes of illness than unipolar patients. It is thus interesting that the present study does not find any significant differences in cognitive function between the two disorders – even without adjusting for differences in the number of episodes. Only the depressive episodes correlated with cognitive impairment, but since unipolar and bipolar patients had had approximately the same number of depressive episodes ($3{\cdot}4 \pm 3{\cdot}5$ *versus* $3{\cdot}3 \pm 3{\cdot}7$ episodes, respectively) unipolar and bipolar patients also exhibited the same severity of cognitive impairment. Interestingly, the magnitude of the effect of the number of episodes

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

was the same in unipolar and bipolar disorder. No other study has compared unipolar and bipolar disorder with regard to cognitive function in the euthymic phase.

Conclusions

The study has tried to avoid the pitfalls of previous studies of cognition in the euthymic phase of affective disorder. Particularly, the study was designed to be representative of patients with moderate to severe affective disorder in general. The cognitive function was assessed diffusely with general neuropsychological measures and adjusted for subclinical psychopathology. In this study a correlation was found between affective disorder in the euthymic phase and cognitive dysfunction. Patients with recurrent episodes were significantly more impaired than patients with a single episode and more impaired than controls and within patients the number of prior episodes seemed to be associated with cognitive outcome. There was no difference in the severity of the dysfunction between unipolar and bipolar patients.

Further confirmation of a correlation between the number of episodes and cognitive impairment is needed in prospectively conducted studies with careful assessment of illness characteristics and treatment, and the psychopathology and cognitive function in the euthymic phase.

This study was supported by: Danish Hospital Foundation for Medical Research; Region of Copenhagen, The Faroe Islands and Greenland; The Foundation for Psychiatric Research (Denmark); The Foundation of Eli and Egon Larsen (Denmark); and The Foundation of Einar Geert-Jørgensen and wife Ellen Geert-Jørgensen (Denmark).

REFERENCES

Abas, M. A., Sahakian, B. J. & Levy, R. (1990). Neuropsychological deficits and CT scan changes in elderly depressives. *Psychological Medicine* **20**, 507–520.

Beats, B. C., Sahakian, B. J. & Levy, R. (1996). Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychological Medicine* **26**, 591–603.

Bech, P. (1988). Rating scales for mood disorders: applicability, consistency and construct validity. *Acta Psychiatrica Scandinavica* **78** (suppl. 345), 45–55.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.

Bulbena, A. & Berrios, G. E. (1993). Cognitive function in the affective disorders: a prospective study. *Psychopathology* **26**, 6–12.

Burt, D. B., Zembar, M. J. & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern and specificity. *Psychological Bulletin* **117**, 285–305.

Calev, A., Korin, Y., Shapira, B., Kugelmass, S. & Lerer, B. (1986). Verbal and non-verbal recall by depressed and euthymic affective patients. *Psychological Medicine* **16**, 789–794.

Coello, E., Ardila, A. & Roselli, M. (1990). Is there a cognitive marker in major depression? *International Journal of Neuroscience* **50**, 137–145.

Coffman, J. A., Bornstein, R. A., Olson, S. S., Schwarzkopf, S. B. & Nasrallah, H. A. (1990). Cognitive impairment and cerebral structure by MRI in bipolar disorder. *Biological Psychiatry* **27**, 1188–1196.

Dupont, A. (1983). A national psychiatric case register as a tool for mental health planning, research, and administration. The Danish model. In *Information Support to Mental Health Programs. An International Perspective* (ed. E. M. Laska, W. H. Gulbinat and D. A. Regier), pp. 257–274. Human Sciences Press: New York.

Folstein, M. F., Folstein, S. E. & McHugh, P. R. (1975). 'Mini-mental state.' A practical method for grading the cognitive state for the clinician. *Journal of Psychiatric Research* **12**, 189–198.

Fromm, D. & Schopflocher, D. (1983). Neuropsychological test performance in depressed patients before and after drug therapy. *Biological Psychiatry* **19**, 55–72.

Gottfries, C. G., Bråne, G. & Steen, G. (1982). A new rating scale for dementia syndromes. *Gerontology* suppl. 2, 20–31.

Hachinski, V. C., Iliff, L. D., Zilhka, E., Du Boulay, G. H., McAllister, V. L., Marshall, J., Russel, R. W. R. & Symon, L. (1975). Cerebral blood flow in dementia. *Archives of Neurology* **32**, 632–637.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–62.

Harvey, P. D., Powchick, P., Parella, M., White, L. & Davidson, M. (1997). Symptom severity and cognitive impairment in chronically hospitalized geriatric patients with affective disorders. *British Journal of Psychiatry* **170**, 369–374.

Hendrie, H. C., Hall, K. S., Brittain, H. M., Austrom, M. G., Farlow, M., Parker, J. & Kane, M. (1988). The CAMDEX: a standardized instrument for the diagnosis of mental disorder in the elderly: a replication with a US sample. *Journal of American Geriatrics Society* **36**, 402–408.

Hennekens, C. H. & Buring, J. E. (1987). *Epidemiology in Medicine*. Little, Brown and Company: Boston.

Huppert, F. A., Brayne, C., Gill, C., Paykel, E. S. & Beardsall, L. (1995). CAMCOG – a concise neuropsychological test to assist dementia diagnosis: sociodemographic determinants in an elderly population sample. *British Journal of Clinical Psychology* **34**, 529–541.

Johnstone, E. C., Owens, D. G. C., Frith, C. D. & Calvert, L. M. (1985). Institutionalisation and the outcome of functional psychosis. *British Journal of Psychiatry* **146**, 36–44.

Kessing, L. V., Dam, H., Jørgensen, O. S. & Bolwig, T. G. (1996). Cognitive impairment in affective disorders. Relation to illness characteristics. *Nordic Journal of Psychiatry* **50**, 305–316.

King, D. A. & Caine, E. D. (1996). Cognitive impairment and major depression: beyond the pseudodementia syndrome. In *Neuropsychological Assessment of Neuropsychiatric Disorders* (ed. I. Grant and K. M. Adams), pp. 200–217. Oxford University Press: Oxford.

La Rue, A., Swan, G. E. & Carmelli, D. (1995). Cognition and depression in a cohort of aging men: results from the Western Colloboratory Group Study. *Psychology and Aging* **10**, 30–33.

Lund, Y., Nissen, M. & Rafaelsen, O. J. (1982). Long-term lithium treatment and psychological functions. *Acta Psychiatrica Scandinavica* **65**, 233–244.

Marcos, T., Salamero, M., Gutierrez, F., Catalan, R., Gasto, C. & Lazaro, L. (1994). Cognitive dysfunctions in recovered melancholic patients. *Journal of Affective Disorders* **32**, 133–137.

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press

McKay, A. P., Tarbuck, A. F., Shapleske, J. & McKenna, P. J. (1995). Neuropsychological function in manic-depressive psychosis. Evidence for persistent deficits in patients with chronic, severe illness. *British Journal of Psychiatry* **167**, 51–57.

Mattis, S. (1976). Mental status examination for organic mental syndrome in the elderly patient. In *Geriatric Psychiatry* (ed. L. Bellak and T. Karasu), pp. 77–121. Grune & Stratton: New York.

Ministry of the Interior (1995). *CRS. The Civil Registration System in Denmark*. Ministry of the Interior: Copenhagen.

Morice, R. (1990). Cognitive inflexibility and pre-frontal dysfunction in schizophrenia and mania. *British Journal of Psychiatry* **157**, 50–54.

Munck-Jørgensen, P., Kastrup, M. & Mortensen, P. B. (1993). The Danish psychiatric register as a tool in epidemiology. *Acta Psychiatrica Scandinavica* suppl. 370, 469–476.

National Board of Health, Denmark (1971). *Classification of Diseases. The Danish edition of ICD-8*. Sundhedsstyrelsen: Copenhagen.

Poon, L. W. (1992). Toward an understanding of cognitive functioning in geriatric depression. *International Psychogeriatrics* **4**, suppl. 2, 241–266.

Post, R. M., Roy-Byrne, P. P. & Uhde, T. W. (1988). Graphic representation of the lifecourse of illness in patients with affective disorder. *American Journal of Psychiatry* **145**, 844–848.

Reisberg, B., Ferris, S. H., de Leon, M. J. & Crook, T. (1988). Global deterioration scale (GDS). *Psychopharmacological Bulletin* **24**, 61–63.

Robbins, T. W., Elliot, R. & Sahakian, B. J. (1996). Neuropsychology – dementia and affective disorders. *British Medical Bulletin* **52**, 627–643.

Roth, M., Thym, E., Mountjoy, C. Q., Huppert, F. A., Verma, S. & Goddard, R. (1986). CAMDEX. A standardised instrument for diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *British Journal of Psychiatry* **149**, 698–709.

Roy-Byrne, P., Port, R. M., Uhde, T. W., Porcu, T. & Davis, D. (1985). The longitudinal course of recurrent affective illness: life chart data from research patients at NIMH. *Acta Psychiatrica Scandinavica* **317**, 3–34.

Sapin, L. R., Berrettini, W. H., Nurnberger, J. I. & Rothblat, L. A. (1987). Mediational factors underlying cognitive changes and laterality in affective illness. *Biological Psychiatry* **22**, 979–986.

Savard, R. J., Rey, R. C. & Post, R. M. (1980). Halstead–Reitan category test in bipolar and unipolar affective disorder. *Journal of Nervous and Mental Disease* **5**, 297–304.

Shaw, E. D., Stokes, P. E., Mann, J. J. & Manevitz, A. Z. A. (1987). Effects of lithium carbonate on the memory and motor speed of bipolar patients. *Journal of Abnormal Psychology* **96**, 64–69.

Tarbuck, A. F. & Paykel, E. S. (1995). Effects of major depression on the cognitive function of younger and older subjects. *Psychological Medicine* **25**, 285–296.

Thamˊ A., Engelbrektson, K., Mathé, A. A., Johnson, L., Olsson, E. & Åberg-Wistedt, A. (1997). Impaired neuropsychological performance in euthymic patients with recurring mood disorders. *Journal of Clinical Psychiatry* **58**, 26–29.

Trichard, C., Martinot, J. L., Alagille, M., Masure, M. C., Hardy, P., Ginestet, D. & Féline, A. (1995). Time course of prefrontal lobe dysfunction in severely depressed in-patients: a longitudinal neuropsychological study. *Psychological Medicine* **25**, 79–85.

World Health Organization (1974). *Glossary of Mental Disorders and Guide to their Classification for use in Conjunction with the International Classification of Diseases, 8th Revision*. WHO: Geneva.

World Health Organization (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. WHO: Geneva.

https://doi.org/10.1017/S0033291798006862 Published online by Cambridge University Press