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ORIGINAL PAPER

Jules Angst · Alex Gamma · Franco Benazzi · Vladeta Ajdacic · Wulf Rössler

Does psychomotor agitation in major depressive episodes indicate bipolarity?

Evidence from the Zurich Study

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Abstract *Background* Kraepelin's partial interpretation of agitated depression as a mixed state of "manic-depressive insanity" (including the current concept of bipolar disorder) has recently been the focus of much research. This paper tested whether, how, and to what extent both psychomotor symptoms, agitation and retardation in depression are related to bipolarity and anxiety. *Method* The prospective Zurich Study assessed psychiatric and somatic syndromes in a community sample of young adults ($N = 591$) (aged 20 at first interview) by six interviews over 20 years (1979–1999). Psychomotor symptoms of agitation and retardation were assessed by professional interviewers from age 22 to 40 (five interviews) on the basis of the observed and reported behaviour within the interview section on depression. Psychiatric diagnoses were strictly operationalised and, in the case of bipolar-II disorder, were broader than proposed by DSM-IV-TR and ICD-10. As indicators of bipolarity, the association with bipolar disorder, a family history of mania/hypomania/cyclothymia, together with hypomanic and cyclothymic temperament as assessed by the general behavior inventory (GBI) [15], and mood lability (an element of cyclothymic temperament) were used. *Results* Agitated and retarded depressive states were equally associated with the indicators of bipolarity and with anxiety. Longitudinally, agitation and retardation were significantly associated with each other (OR = 1.8, 95% CI = 1.0–3.2), and this combined group of major depressives showed stronger associations with bipolarity, with both hypomanic/cyclothymic and depressive temperamental traits, and with anxiety. Among agitated, non-retarded depressives, unipolar mood disorder was even twice as common as bipolar mood disorder. *Conclusion* Combined agitated and retarded major depressive states are more often bipolar than unipolar, but, in general, agitated depression (with or without retardation) is not more frequently bipolar than retarded depression (with or without agitation), and pure agitated depression is even much less frequently bipolar than unipolar. The findings do not support the hypothesis that agitated depressive syndromes are mixed states. *Limitations* The results are limited to a population up to the age of 40; bipolar-I disorders could not be analysed (small N).

Key words agitation · retardation · bipolar disorder · major depression · mixed state · anxiety

J. Angst (✉) · A. Gamma · F. Benazzi · V. Ajdacic · W. Rössler
Psychiatric Hospital
Zurich University
Lenggstrasse 31
P.O. Box 1931
8032 Zurich, Switzerland
Tel.: +41-44/384-2611
Fax: +41-44/384-2446
E-Mail: jangst@bli.uzh.ch

F. Benazzi
Hecker Psychiatry Research Center at Forli
Forli, Italy

F. Benazzi
Department of Psychiatry
National Health Service
Forli, Italy

Introduction

Psychomotor agitation and retardation are elements of the diagnostic criteria for major depressive episodes (MDE) in DSM-IV-TR [2] and ICD-10 [42]. In both diagnostic manuals, bipolar MDE and unipolar MDE are assumed to have similar clinical features, and there is no specific distinction made between agitated and retarded MDE.

Historically, agitated depression was first considered to be a subtype of melancholia (melancholia agitans) often associated with anxiety (Kahlbaum [23], Griesinger [22]). Kraepelin [26], too, shared this view in his first compendium of psychiatry. Weygandt's [41] large monograph on mixed states distinguished between agitated depression as a frequent

manifestation of involutional melancholia and agitated depression as a mixed state. In the seventh edition of his influential textbook on psychiatry, Kraepelin [28], following Weygandt, interpreted agitated depression only partially as a mixed state of circular depression within "manic-depressive insanity". And in the eighth edition Kraepelin warned against a dubious simplistic view which interpreted all agitated depressive states as mixed states and explicitly stressed the correlation between anxious agitated depressive states and age [29, 38].

There are two sides to the question of the relationship between agitation and depression: first, are agitated depressive states more frequently bipolar (e.g. mixed) or unipolar? And second, are unipolar or bipolar states more frequently agitated or retarded? These are theoretically distinct issues that depend on the actual frequency of unipolar and bipolar depression. However, given that BP disorders are about equally or less frequent than major depression, it follows that if agitated depressions were mainly bipolar (e.g. a mixed state of bipolar disorders), they should also be more common in bipolar than unipolar depression.

But some clinical descriptions comparing bipolar depression (mainly in bipolar-I disorder (BP-I)) with unipolar depression reported that retardation was more common in bipolar depression and agitation more frequent in unipolar depression (review by Goodwin and Jamison [20]). A recent review supported these psychomotor differences [32] but noted that, in contrast to BP-I, bipolar-ii disorder (BP-II) may instead have more psychomotor agitation than retardation; this is in agreement with the view of Parker, who studied melancholia very carefully quantifying the motor activity [34, 35].

In a first study Maj et al. [30] found agitated depression in around 20% of 122 BP-I patients; almost two thirds of agitated depressive syndromes were mixed depression (i.e. had at least two concurrent manic symptoms). Agitated depressives were more severely ill in terms of the number of symptoms and number of hospitalisations before the index episode, spent more time in episodes during the follow-up than non-agitated BP-I depressives but had similar outcomes. In a second study of patients with agitated major depressive disorders Maj et al. [31] found only 25 of 94 patients (27%) with two or more hypomanic/manic symptoms suggesting the presence of mixed or bipolar states. These 25 patients differed from the other 69 patients in their higher rates of positive family history for bipolar disorder and suicide attempts and a longer duration and greater severity of episodes. Koukopoulos et al.'s [25] review of mixed depression also supported its bipolar association. Agitated depression in BP-II and MDD was studied by Benazzi [8, 9, 12], who confirmed that it was only partially a mixed depressive syndrome of bipolar nature.

According to Goodwin and Ghaemi [18] the diagnostic validity of agitated depression for bipolarity would be supported if it were shown that the association was independent of a mixed state. However, Benazzi tested this hypothesis in a large BP-II and MDD sample [9] and showed that on certain diagnostic validators (e.g. BP family history, early age of onset) agitated and non-agitated depression (MDE) differed only when agitated depression was mixed with manic symptoms (which was often the case). Summarising the literature recently Goodwin and Jamison [21] concluded that an elevated risk for bipolarity in first degree relatives of agitated unipolar patients is no adequate basis for designating such patients as bipolars per se [19].

In this paper we present data from the prospective Zurich Study collected over a period of 20 years. In contrast to other analyses, our aim is to test whether, how, and to what extent both agitated and retarded depression are related to bipolarity. If agitated, as against retarded, depression represented a mixed state, it should be significantly more associated with indicators of bipolarity, retarded depression never having been considered to be a mixed state. As indicators of bipolarity we will use a positive family history of bipolarity and temperamental traits (cyclothymic, hypomanic, "ups & downs" in mood). The analysis will deal with major uni- and bipolar II depressive episodes (MDE) and include milder uni- and bipolar depressive episodes.

Methodology

Sample

The Zurich Study (a prospective epidemiological study of depressive, neurotic and psychosomatic syndromes) was based at outset on a sample of 4,547 young subjects (m = 2,201; f = 2,346) representative of the canton of Zurich in Switzerland in 1978 (population 1.1 million). All subjects were screened with the Symptom Checklist 90-R (SCL-90-R) [16], a comprehensive self-report questionnaire of 90 questions, validated for screening purposes and covering a broad range of psychiatric symptoms. The screening took place in 1978, when the male participants were aged 19 (at conscription) and the females 20 (at enrolment on the electoral register). In order to enrich the sample with cases at risk for the development of psychiatric syndromes, a stratified sampling procedure was chosen: a sub-sample of 591 subjects (292 males, 299 females) was selected for interview, with two-thirds consisting of high scorers (i.e. above the 85th percentile on the Global Severity Index of the SCL-90), and one-third being a random sample of those with lower scores (below the 85th percentile). The stratified sample represents 2,600 persons of the same age from the general population. The theoretical basis of these stratified procedures is described by Dunn et al. [17]. There were no gender differences in socio-demographic characteristics.

Details of sampling procedures and refusal rates were presented in the first publication [4] and recently again [7].

Interview

The structured psychopathological interview and rating of social consequences of psychic disturbances for epidemiology (SPIKE) was used [4]. Since screening in 1978, six interview waves have been conducted: in 1979 (subjects' age 20(m)/21(f)), 1981 (22/23),

1986 (27/28), 1988 (29/30), 1993 (34/35) and 1999 (40/41). Interviews were administered in the participants' homes by psychiatrists and clinical psychologists with extensive clinical training [3].

Validity and reliability testing has been carried out with particular reference to depression and anxiety and their symptoms, including agitation and retardation [7].

At the age of 27/28 the subjects' family histories were assessed for 24 somatic and psychiatric syndromes using a detailed list of all first degree relatives, which was checked in the context of every interview section. An operationalised diagnosis among relatives was not made, and children were not included because of their young age. A positive family history for suicidality required the presence of suicide attempts or suicides.

In the section on hypomania/mania all subjects were asked whether, during the previous 12 months, they had experienced a period of increased initiative, activity, less need for sleep, being less tired, more talkative, travelling more etc. and whether this had been so intense that they had experienced financial problems or difficulties with others. They were also asked whether other people had noticed such periods in them.

If an interviewee reported depression, 28 symptoms, the episode's duration and recency, and, if applicable, the number of episodes over the previous twelve months were assessed. In addition, subjects were asked their age at the first episode of such a diagnostically unspecified depressive syndrome as described in the stem and additional 28 symptom questions. Age of onset therefore refers to a diagnostically unspecified depressive syndrome described by the patient as an episode of depression.

In contrast to clinical studies, whose subjects at outset are sick, an epidemiological sample is examined independently of the presence or absence of psychopathology. The methodological question is whether critical responses by interviewees are state-dependent. For each of the five interviews we analysed whether the rates of agitation and retardation were dependent on the recency of the depressive episode over the previous 12 months, by comparing depressives who had suffered from an MDE during the previous 4 weeks (point prevalence) with those whose depression had occurred at some time during the 11 months prior to that. All comparisons were non-significant; rates of agitation and retardation were independent of the recency of the MDE episodes. The same result was obtained when all diagnoses of milder depression were included (dysthymia, minor depression and recurrent brief depression).

In the interview section on anxiety states 21 symptoms were assessed. The diagnosis of GAD and panic disorder based on DSM-III criteria.

Definitions

Psychomotor symptoms were assessed within the interview on depressive symptoms. Agitation was defined as motor restlessness with sustained movements, and retardation as observable slowing of movements and speech. BP-I was defined by DSM-IV criteria, BP-II by broad Zurich criteria, requiring 2 of 7 symptoms of DSM-IV hypomania with a minimum duration of one or more days [5]. Minor bipolar disorders (MinBP) required the broad Zurich criteria for hypomania plus (1) dysthymia (DSM-III-R), (2) minor depression required a minimum duration of 2 weeks plus 3–4 of 7 DSM-III-R criterial symptoms for depression or (3) recurrent brief depression defined by five or more criterial symptoms of depression, a duration of 1–13 days, with at least monthly recurrences plus associated with work impairment. Atypical depression was defined by DSM-IV criteria.

Indicators and other variables

As bipolar indicators we used (1) a family history of mania/hypomania, (2) a diagnosis of BP-II, (3) cyclothymic/hypomanic temperament as measured by the general behavior inventory (GBI) at age 27/28. The GBI has been diagnostically validated in unipolar and bipolar patients [14]. A fourth indicator was mood lability, defined as a personality trait (frequent "ups & downs") as assessed at the last three interviews (1988–1999). Many studies have demonstrated an association between cyclothymic/hypomanic temperament, including ups and downs, and bipolar disorder [1]. As further indicators we used age of onset and course in terms of percentage of years in which subjects manifested depressive symptoms. Treatment rates refer to professional treatment by MDs or psychologists during the twelve months prior to the interviews. Distress was assessed by a visual analogue scale (0–100). From 1986 to 1999 (four interviews) 27 depressive symptoms were assessed; their sum score is taken as one measure of severity.

Statistics

χ^2—tests were used for categorical variables. Kruskal–Wallis tests were applied to rank-ordered data.

Three separate logistic regression analyses were conducted for the dependent variables agitated MDE, retarded MDE, and agitated + retarded MDE. The same independent variables were used in each analysis: BP-II, age of onset of depressive/hypomanic syndrome, hyperthymic or cyclothymic temperament, a family history of bipolar disorder, and the percentage of years with depressive symptoms relative to the total number of years of follow-up including the retrospectively assessed years between interviews.

A further three logistic regressions were run with atypical MDE as the dependent variable, this time with three different, but overlapping sets of independent variables: presence of agitation, gender and BP-II; presence of retardation, gender and BP-II; and longitudinal presence of both agitation and retardation, gender and BP-II.

Analyses were carried out in SAS 8.2 for Windows and Stata 8.2 for Windows.

Given the large number of comparisons, Bonferroni correction was applied to reduce the risk of type I error (i.e. chance significant findings). Since strict Bonferroni correction is overly conservative, we applied it separately to families of tests constituting a distinct, circumscribed analysis. These analyses correspond to the Tables 1, 2, 3 and 4 with Table 3 consisting of two analyses (MDE, and other depression).

Results

In a first step we present the chosen indicators of bipolarity applied to the mood spectrum, in order to check their suitability for further analyses.

Comparative validity of six diagnostic subgroups of mood disorder

Table 1 shows six different subgroups of mood disorder: DSM-IV bipolar-I disorder, bipolar-II disorder defined by broad Zurich criteria, minor bipolar disorder (MinBP), hypomania, major depressive disorder (MDD) and other depressive disorders (dysthymia, minor depression and recurrent brief depression). Subjects with a diagnosis of bipolar disorder or of hypomania had significantly higher rates of a positive family history of mania. A family history of depression was high in all groups with mood disorders, except for hypomanics and controls.

Temperament (measured by the GBI) and mood lability (ups and downs) as a trait were strongly

Table 1 Family history, age of onset, mood lability and temperament as indicators of mood disorders and symptoms. *P*-Values significant after Bonferroni correction are printed in bold (threshold: $P = 0.0024$, 21 tests)

	BP-I DSM 1	BP-II ZHR 2	MinBP 3	Hypo-mania 4	MDD 5	Other Depr. 6	Others 7	*P* 1–7	*P* 1–2	*P* 1, 2, 5
Prevalence (%)	2.2	9.3	9.4	3.3	11.4	13.2	51.2			
N	15	78	59	23	101	85	230			
FH+ (%)										
Mania	33.3	13.2	10.5	19.1	3.5	3.1	5.1	**0.0003**	0.05	**0.001**
Depression	73.3	60.3	67.8	21.7	64.4	47.1	29.1	**0.0001**	0.34	0.60
Course										
Age of onset (means, SD)	12.4 (5.07)	13.9 (5.41)	14.2 (4.33)	16.4 (4.76)	14.4 (5.15)	16.3 (4.83	16.3 (5.14)	**0.0003**	0.32	0.37
% years depressed	66.8	57.3	57.4	30.4	55.4	47.0	29.0	**0.0001**	0.21	0.37
Temperament										
GBI										
Hypom./cyclo means (SD)	7.1 (5.1)	4.0 (3.8)	4.2 (3.6)	3.4 (2.2)	2.4 (3.2)	2.9 (3.2)	1.3 (1.9)	**0.0001**	0.02	**0.0002**
Depressive means (SD)	11.2 (9.56)	7.8 (8.44)	6.9 (7.86)	1.9 (2.48)	5.0 (6.42)	4.7 (6.39)	1.3 (2.31)	**0.0001**	0.15	0.01
Ups & downs in mood (%)	40.0	35.9	32.2	4.4	19.8	10.6	5.7	**0.0001**	0.76	0.03

Table 2 Agitated and retarded major depressive episodes (MDE): diagnoses, family history, course and temperament. *P*-Values significant after Bonferroni correction are printed in bold (threshold: $P = 0.0017$, 30 tests)

	Agitated	Non-agitated	*P*	Retarded	Non-retarded	*P*
MDE	112	78		93	97	
%						
BP-I (small $N = 15$)	(7.1)	(8.9)	(0.65)	(10.6)	(5.1)	(0.15)
BP-II ($N = 78$)	43.8	37.2	0.37	50.5	32.0	0.009
MDD ($N = 99$)	50.0	55.1	0.49	39.8	63.9	**0.0009**
FH+						
Mania	7.8	12.7	0.29	12.2	7.1	0.26
Depression	68.8	57.7	0.12	67.7	60.8	0.32
Comorbidity						
GAD	37.5	23.1	0.04	36.6	26.8	0.15
Panic disorder	17.9	7.7	0.05	15.1	12.4	0.59
Panic attacks	41.1	21.8	0.005	39.8	26.8	0.06
Number of symptoms (max of four interviews 1986–1999) (means (SD))						
Depression (total: 27)	17.7 (4.7)	13.9 (5.7)	**0.0001**	18.4 (3.9)	13.8 (5.9)	**0.0001**
Anxiety (total: 21)	10.9 (5.4)	8.8 (4.3)	0.03	11.6 (5.2)	8.4 (4.5)	**0.0003**
Course (means(SD)						
Age of onset (means, SD)	13.5 (5.0)	14.7 (5.6)	0.05	13.2 (5.3)	14.8 (5.2)	0.02
% years depressed over 22 years	63.7 (25.6)	52.6 (26.2)	0.005	64.7 (25.0)	53.9 (26.7)	0.004
Temperament						
GBI						
Hypom./cyclo. means (SD)	3.9 (4.3)	2.6 (2.9)	0.07	4.2 (4.3)	2.6 (3.0)	0.03
Depressive means (SD.)	8.0 (8.8)	4.5 (5.4)	0.01	8.3 (8.4)	4.8 (6.5)	0.002
Ups & downs in mood (%)	32.1	23.1	0.18	34.4	22.7	0.08

Data only shown for completeness; includes two cases without MDE that not included in the total MDE count (but used to compute the correct percentages). The symptoms "agitation" and "retardation" are not included

associated with the diagnosis of bipolarity. BP-I subjects scored generally higher than BP-II subjects, while MDD subjects consistently scored lowest; this was true for both hypomanic/cyclothymic and depressive features in the GBI [14].

Agitated and retarded depressive syndromes

In order to make our analyses comparable to other studies we present data on agitated vs. non-agitated MDE subjects and on retarded vs. non-retarded MDE subjects. These first comparisons disregard the fact that the groups of agitated and retarded subjects are not mutually exclusive: longitudinally, 61 subjects exhibited both types of symptoms, being in one episode agitated-depressed and in another retarded-depressed. The OR of this longitudinal association was significant (OR = 1.8, 95% CI = 1.0–3.2, $P = 0.05$).

Agitated depression was not uncommon in this epidemiological sample; cumulatively across five interviews it was as frequent in MDD (55.5%) as in BP-II (61.8%, $P < 0.39$). Retarded depression was cumulatively present in 60.7% of BP-II and in 36.6% of MDD subjects ($P < 0.001$). Comparatively the average annual rates for both agitated and retarded MDE were considerably lower: 39.9% (range 34.6–52.5%) and 33.6% (range 27.1–42.5%).

Table 2 shows BP-II and MDD subjects to be about equally represented in agitated and non-agitated

Table 3 Agitation and retardation: family history, age of onset and temperament in subjects with major depressive episodes (MDE) and other types of depression (dysthymia, recurrent brief depression and minor depression). *P*-Values significant after Bonferroni correction are printed in bold (threshold for MDE analysis: $P = 0.0017$, 30 tests; threshold for analysis of other depression: $P = 0.0021$, 24 tests)

	Agitated + retarded	Agitated	Retarded	Neither	*P*	
	1	2	3	4	1–4	2–3
MDE	61	51	32	46		
BP-I ($N = 15$)	(11.3)	(2.0)	(9.4)	(8.5)	(0.31)	(0.13)
BP-II ($N = 78$)	55.7	29.4	40.6	34.8	0.03	0.03
MDD ($N = 99$)	34.4	68.6	50.0	58.7	0.003	0.003
FH+ (%)						
Mania	11.9	2.3	12.9	12.5	0.29	0.07
Depression	70.5	66.7	62.5	54.4	0.37	0.70
Comorbidity						
GAD	42.6	31.4	25.0	21.7	0.11	0.53
Panic disorder	19.7	15.7	6.3	8.7	0.21	0.20
Panic attacks	47.5	33.3	25.0	19.6	0.02	0.42
Suicide attempts	29.5	23.5	21.9	21.7	0.77	0.86
Number of symptoms (max of 4 interviews 1986–1999) (means (SD))						
Depression (total: 25)	19.4 (3.5)	15.6 (5.2)	16.6 (3.9)	11.9 (6.0)	**0.0001**	0.53
Anxiety (total: 21)	12.5 (5.3)	8.5 (4.6)	9.5 (4.1)	8.2 (4.5)	**0.0006**	0.36
Course (means (SD))						
Age of onset	13.3 (4.91)	13.8 (5.05)	13.0 (5.95)	16.0 (5.09)	0.01	0.51
% years depressed over 22 years	66.7	54.4	54.0	46.9	0.002	0.91
Temperament						
GBI						
Hypom./cyclo.	4.8 (4.61)	2.8 (3.50)	3.0 (3.51)	2.3 (2.32)	0.04	0.90
Depressive	10.2 (9.24)	5.1 (7.21)	4.7 (4.92)	4.5 (5.75)	**0.0008**	0.68
Ups & downs	36.1	27.5	31.3	17.4	**0.0001**	0.72
Other depres.	32	40	21	46		
FH+ (%)						
Mania	6.5	8.3	5.0	8.1	0.97	0.65
Depression	78.1	55.0	57.1	47.8	0.06	0.83
Comorbidity						
GAD	34.4	17.5	28.6	19.6	0.31	0.32
Panic disorder	21.9	10.0	4.8	4.4	0.07	0.48
Panic attacks	34.4	30.0	33.3	15.2	0.19	0.79
Suicide attempts	12.5	7.5	9.5	6.5	0.81	0.78
Number of symptoms (max of four interviews 1986–1999) (means (SD))						
Depression (total: 27)	17.2 (4.9)	13.2 (5.7)	14.6 (5.2)	8.5 (5.9)	**0.0001**	0.36
Anxiety (total: 21)	12.8 (4.6)	8.1 (3.9)	7.6 (3.8)	6.7 (3.3)	**0.0001**	0.68
Course (means (SD))						
Age of onset	14.9 (4.88)	16.4 (5.26)	14.4 (1.87)	15.7 (4.92)	0.35	0.16
% years depressed over 22 years	60.6	55.3	57.0	36.7	**0.0001**	0.73
Temperament						
GBI						
Hypom./cyclo.	4.4 (3.98)	4.0 (2.93)	2.9 (4.14)	2.9 (3.21)	0.05	0.04
Depressive	8.7 (9.31)	6.9 (7.37)	4.3 (6.01)	3.5 (4.95)	**0.0001**	0.07
Ups & downs (%)	34.4	22.5	19.1	8.7	0.05	0.76

Data only shown for completeness; includes two cases without MDE that not included in the total MDE count (but used to compute the correct percentages) The symptoms ''agitation'' and ''retardation'' are not included

Table 4 Severity of agitated and retarded MDE. P-Values significant after Bonferroni correction are printed in bold (threshold: $P = 0.0036$, 14 tests)

	Agitated + retarded 1	Agitated 2	Retarded 3	Neither 4	*P* 1–4	*P* 1–3
MDE	61	51	32	46		
Number of depressive symptoms (total: 25)[a] (means (SD))	19.4 (3.5)	15.6 (5.2)	16.6 (3.9)	11.9 (6.0)	**0.0001**	0.53
Number of diagnostic symptoms (total: 8)[a] (means (SD))	7.2 (.8)	6.5 (1.2)	6.5 (1.1)	6.5 (1.1)	**0.0001**	**0.0002**
Distress (means (SD))	84.4 (16.6)	81.7 (18.9)	83.5 (12.4)	84.2 (16.9)	0.52	0.74
%						
Work impairment[b]	86.7	79.2	71.9	69.1	0.15	0.54
Social impairment[b]	98.3	87.5	96.9	78.6	0.004	0.07
Any impairment[b]	100.0	93.8	100.0	81.0	**0.0004**	0.02
Treated[c]	62.3	54.9	53.1	37.0	0.08	0.17

[a]The symptoms ''agitation'' and ''retardation'' are not included
[b]1986–1999
[c]During interview years

MDE. Surprisingly, in the retarded group there were more BP-II (50% vs. 32%) and in the non-retarded group significantly more MDD disorders (32% vs. 64%). The other indicators of bipolarity (a positive family history of mania, cyclothymic/hyperthymic temperament, mood lability) tended also to be more present in both agitated and retarded depressives than in subjects without psychomotor symptoms. But the differences became insignificant by the Bonferroni correction.

Similar findings were seen in multivariable logistic regression analyses. Agitated MDE was not associated with BP-II or hypomanic/cyclothymic temperament, while retarded MDE tended to be associated with BP-II (OR 1.8, 95% CI = 0.96–3.6, $P = 0.07$).

Agitated and retarded depression in relation to the indicators of bipolarity

In a next step we repeated the analyses, comparing four groups: depressed subjects (1) with both agitation and retardation (either simultaneously or in succession), (2) agitation only, (3) retardation only and (4) others.

A longitudinal presence of both agitation and retardation was significantly ($P < 0.004$) more common among the 78 BP-II (43.8%) than the 99 MDD subjects (21.2%), whereas agitation alone was more present in MDD (35.4%) than BP-II (18.0%). Retardation alone was equally present in BP-II (16.9%) and in MDD (16.2%); (Table not shown). The combined group manifesting agitation and retardation comprised a higher proportion of BP-II than MDD cases. For the pure groups, the pattern was reversed: both the purely agitated and the purely retarded depressive group comprised more MDD cases. The difference was particularly striking for the purely agitated group. The combined group also had a stronger association with bipolar temperamental measures than the two pure groups (Table 3). In logistic regression analysis, this group showed significant associations with both BP-II (OR = 2.3, 95% CI = 1.1–4.7, $P = 0.02$) and hypomanic/cyclothymic temperament (OR = 1.1, 95% CI = 1.0–1.2, $P = 0.04$). It was also characterised by higher severity in terms of total number of depressive and anxiety symptoms. Agitated and retarded major depressives did not differ in terms of anxiety symptoms, although panic disorders and attacks tended to be more common among agitated depressives (P = NS).

Table 3 presents the results for two diagnostic groups: subjects with MDE and those with milder depression (dysthymia, recurrent brief depression and minor depression). Within both diagnostic groups the purely agitated and purely retarded depressives had similar rates of a family history of mania and depression. A family history of mania tended to be more frequent in purely retarded MDE. The age of onset in subjects with agitated or retarded depression was also not significantly different. Among MDE subjects there were no differences in temperamental traits, whereas among the milder depressions agitated depressives showed a trend to higher scores on temperamental measures than retarded depressives. There were no differences in lifetime rate of suicide attempts between purely agitated and purely retarded depressives, neither in major nor in milder depression.

Agitation and retardation in relation to atypical depression

DSM-IV atypical depression was diagnosed in 47 subjects and was equally present in agitated and non-agitated MDE (26.9 and 24.3% respectively, $P < 0.70$); the same was true for retarded and non-retarded MDE (29.4 and 22.2% respectively, $P < 0.28$). Atypical depression was also virtually equally present in subjects with BP-II and those with MDD (20.7 and 29.4% respectively, $P < 0.13$); at least there was no evidence of atypical depression being over-represented among BP-II subjects. Application of logistic regression to atypical MDE revealed no significant associations with agitation and retardation (either separate or in combination), with gender or with BP-II.

Agitation and retardation in relation to the severity of depression

The severity of depression was measured by the total of 25 assessed symptoms, by the eight diagnostic symptoms (in both cases agitation and retardation were excluded as symptoms), by maximum severity of distress on a visual analogue scale (0–100), by work, social and any impairment, and by treatment rates.

The results are shown in Table 4. Subjects with psychomotor symptoms suffered more from depressive symptoms than those without psychomotor symptoms; they also showed a trend to higher rates of treatment and impairment but did not differ in distress rates.

Subjects with both agitated and retarded MDE scored highest on all measures of severity.

Discussion

The present study found no evidence that agitated depression is exclusively or even mainly a bipolar mixed state. Agitated major depressive states were no more frequently bipolar than they were unipolar, and retarded depressive states were as frequently bipolar as were agitated depressive states. Conversely, agitated depression was not significantly more frequent in bipolar-II compared to unipolar MDE.

Agitated depression was on average present in 40% of MDE subjects per interview across five waves; the cumulative rate was 59%. The corresponding figures for retardation were 34% per interview and 49% cumulatively. Unexpectedly, agitation was found with equal frequency in MDD (55.5%) and BP-II disorders (61.8%), whereas retardation was more common in BP-II (60.7%) than in MDD (36.6%). This finding disconfirms several recent clinical studies, which reported agitation as being more common among bipolar patients (reviewed by Benazzi [11, 13]). However, it is in line with classical findings in comparisons of BP-I and MDD (reviewed by Goodwin and Jamison [21]; Mitchell and Malhi [32]) and extends those findings to BP-II. It is also compatible with Parker's studies [35], which have shown agitated depression to be equally frequent in MDD and BP-II. In our sample BP-II depressive subjects were more likely than MDD subjects to manifest psychomotor changes (agitated depression alternating with retarded depression during follow-up) (44% vs. 21%), suggesting that psychomotor change is more a feature of bipolar than of unipolar disorders. Of course the chance of developing both forms of motor symptoms is a function of periodicity, which is higher among bipolar than major depressive disorders.

Psychomotor signs (agitation and retardation) are key features of melancholia [35, 40]. In the present study MDE subjects with psychomotor signs shared many characteristics: compared to MDE subjects without such signs they tended to be more severely ill, to have manifested their first diagnostically unspecified depressive syndrome at an earlier age, to be more often symptomatic across 22 years, to have suffered from more symptoms and to be more often treated and more frequently impaired. They were also more characterised by depressive and cyclothymic personality traits. But due to the Bonferroni correction for multiple testing some results became statistically non-significant. Nevertheless the described tendencies are compatible with the Australian studies of melancholics [33, 36] and with Maj's findings in agitated bipolar-I patients [30].

There is a vast literature demonstrating the association between cyclothymic/hypomanic temperament, including "ups and downs", with bipolar disorder [1, 14]. Our results in Table 1 confirm this clearly, and on that basis, together with a family history of mania, we chose those temperamental traits as indicators of bipolarity. An important result of our study is that both psychomotor signs agitation and retardation had an equal affinity to temperamental indicators of bipolar disorder. This new finding, which is analogous to the reports of the classical studies on BP-I depression, may be a consequence of the nature of the present epidemiological sample, and may therefore differ from the clinical studies reported above.

On the evidence from our study, agitated depression is not diagnostically more specific for a bipolar spectrum disorder than retarded depression. Given the lack of differences between agitated and retarded depression, one cannot conclude that agitated depression is usually a bipolar mixed state. Our interpretation concurs with Kraepelin's earliest and latest view of the matter [26, 27] and with Goodwin and Jamison [21], cited above, that agitated depression can occur in two ways, as a mixed state and as an anxious syndrome of unipolar depression.

Our findings are also in line with the frequent observation of psychomotor agitation in many Axis I and Axis II disorders [2], suggesting that it is rather non-specific from a nosological point of view. Although psychomotor signs are considered to be characteristic for melancholic MDE, there is no convincing evidence that melancholia is much more than a typical severe form of depression [6]. Our data also do not support the view that agitated depression is associated with symptoms or a diagnosis of anxiety (GAD, panic disorder), because the average sum of anxious symptoms was the same in retarded (9.5) and agitated depressives (8.5). Our finding is restricted to subjects up to age 40 and does not exclude an association in older subjects as observed by Kraepelin.

However, a special feature of the study is its representativeness up to the age of 40/41, being an epidemiological sample studied prospectively, while previous reported findings were based mainly on treated samples and were usually cross-sectional. The study also illustrates how essential it is to base on multiple indicators of validity; this is in agreement with the recent warnings of Kendler [24] regarding the current limits of genetic validators and the importance of homogeneous phenotypes for analyses, as stressed by Rietschel et al. [37] in their reply to Kendler's warnings.

Summing up, many of our findings are negative. Neither was bipolarity more common in agitated depression than unipolarity, nor was agitated depression more common in bipolar than in major depressive disorders. We thus found no evidence for the view that agitated depression is exclusively a mixed state of bipolar disorder in our community sample. Both agitation and retardation were equally associated with bipolar indicators, supporting the view that psychomotor symptoms in general are common in bipolar disorder. Furthermore, compared to retarded depression agitated depression was not characterised by higher anxiety. A useful avenue of research would be to replicate these findings in bipolar-I subjects in large community samples. This would clarify the role of severity of the bipolar component in its association with psychomotor signs [10].

Limitations

Our study was not specially designed for the question analysed here, therefore we have no quantitative

measures of agitation and retardation. Compared to recent studies reported in the Introduction, it was not possible to analyse data on manic/hypomanic symptoms concurrent with depressive syndromes (i.e. mixed depression). Our relatively small community sample represents only the ages up to 40 and the bipolar-I group was too small for statistical analyses. A further methodological limitation is that the bipolar family history was not assessed blindly by a validated instrument, as in most of the clinical studies above. Healthy subjects tend to significantly under-report a positive family history compared to subjects who have experienced depression, bipolar disorder or anxiety themselves [39] but this bias does not apply to our comparison of retarded and agitated depression. In addition not all depressive subjects were actually depressed when they were interviewed, because the interview covered the past 12 months; but we could not find any relevant bias induced by that.

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