Recurrent brief depressive disorder reinvestigated: a community sample of adolescents and young adults

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ABSTRACT

Background. This article presents prospective lower bound estimations of findings on prevalence, incidence, clinical correlates, severity markers, co-morbidity and course stability of threshold and subthreshold recurrent brief depressive disorder (RBD) and other mood disorders in a community sample of 3021 adolescents.

Method. Data were collected at baseline (age 14–17) and at two follow-up interviews within an observation period of 42 months. Diagnostic assessment was based on the Munich Composite International Diagnostic Interview (M-CIDI).

Results. Our data suggest that RBD is a prevalent (2.6%) clinical condition among depressive disorders (21.3%) being at least as prevalent as dysthymia (2.3%) in young adults over lifetime. Furthermore, RBD is associated with significant clinical impairment sharing many features with major depressive disorder (MDD). Suicide attempts were reported in 7.8% of RBD patients, which was similar to MDD (11.9%). However, other features, like gender distribution or co-morbidity patterns, differ essentially from MDD. Furthermore, the lifetime co-occurrence of MDD and RBD or combined depression represents a severe psychiatric condition.

Conclusions. This study provides further independent support for RBD as a clinically significant syndrome that could not be significantly explained as a prodrome or residual of major affective disorders.

INTRODUCTION

Concept and previous findings

Since the introduction of explicit symptom and duration criteria for mood disorders in ICD-10 and DSM-IV, the appropriateness of these threshold definitions for specific disorders has been investigated in several studies (Wittchen *et al.* 1998*a, b*, 2000; Angst *et al.* 2000*a, b*). At the core of these findings stands the repeated demonstration that even patients who fall short of stringent diagnostic criteria (e.g. major

depressive disorder (MDD)) reveal substantial suffering, impairment and correlates of clinical significance such as increased incidence of suicide attempts. Thus, boundaries of disorders within the mood disorder spectrum, as well as their delineation from other disorders, are not yet resolved (Kendler & Gardner, 1998).

Among the many attempts to identify such clinically significant expressions of mood disorders recurrent brief depressive disorder (RBD) has evolved as a particularly promising concept (Angst *et al.* 2000*b*; Kasper *et al.* 2000; Pezawas *et al.* 2001). RBD has been defined by presenting the same full-blown picture of depression as MDD, but failing to meet the mandatory 2 weeks duration criterion. Additionally, brief depressive

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episodes have to occur about monthly, being independent of the menstruation cycle within an observation period, lasting 12 months.

The clinical significance and supportive validation work on RBD has been reported in psychiatry for more than a century (Angst, 1994*a*). An operationalized definition of RBD has been introduced in 1985 referring to the results of the Zurich-Study (Angst & Dobler-Mikola, 1985). During this observation period a 9.8% lifetime prevalence of RBD (Angst, 2000*a*) similar to MDD has been found. In this study the syndromal and associated features of RBD, sufficiently unique patterns of course and its clinical significance in terms of impairment and various clinical correlates have been worked out (Angst, 1994*b*). The particularly high suicide attempt risk of subjects with RBD was noted. These findings have been supported by a comprehensive World Health Organization (WHO) project on 'Psychological problems in general health care' and further associated studies (Sartorius *et al.* 1993) in primary care settings. Notably, two centres confirmed patterns of clinical significance in this study (Maier *et al.* 1994*a, b*; Weiller *et al.* 1994*a*). Furthermore, prevalence rates of RBD are available for 15 different international primary care settings ranging from 3.7% to 5.7% (Weiller *et al.* 1994*b*). Also, results of an independent general population survey in Sardinia revealed as well a high lifetime prevalence (6.9%) of RBD associated with an increased suicide risk and alcohol abuse (Altamura *et al.* 1995). However, a contradictory low clinical prevalence rate (2%) was reported in the DSM-IV Mood Disorder Field Trial (Keller *et al.* 1995).

Subsequently, other studies including a community enquiry (Snaith, 2000) have provided substantial further evidence of RBD in terms of clinical validation in studies on seasonal patterns of RBD (Kasper *et al.* 1994), and the provision of biological support (Montgomery *et al.* 1989; Staner *et al.* 1992; De la Fuente *et al.* 2002; Pezawas *et al.* 2002*a*). Retrospectively evaluated patterns of duration in epidemiological studies have been supported by prospective clinical studies (Post *et al.* 1998; Pezawas *et al.* 2002*b*). Additionally, several controlled treatment studies (Montgomery *et al.* 1994; Kocmur *et al.* 1998; Pazzaglia *et al.* 1998; Verkes *et al.* 1998; Wermuth *et al.* 1998), one open trial (Stamenkovic *et al.* 2001), one single case analysis

(Pezawas *et al.* 2002*b*) and case reports (Gertz, 1992; Joffe, 1996; Amore *et al.* 1998; Corominas *et al.* 1998; Stamenkovic *et al.* 1998) investigated drug response in RBD and documented the need for treatment. The clinical significance of this diagnostic concept has further been underlined by studies on patterns and consequences of a lifetime co-occurrence of both, RBD and MD, called combined depression (CD) (Montgomery *et al.* 1989), which has been further developed by Angst (1990). Epidemiological (Angst, 1994*b*; Maier *et al.* 1994*a*) and clinical (Montgomery *et al.* 1989; Pezawas *et al.* 2002*a*) studies demonstrated a dramatic increase of suicide attempt rates and measures of impairment in the case of CD in comparison to either single RBD or MD.

Based on such epidemiological findings RBD has been integrated as a distinct mood disorder diagnosis into ICD-10 and as research diagnosis in the appendix of DSM-IV with the need of systematic future research to support the independent status of RBD. Nevertheless, some significant reservations regarding RBD as an independent and new diagnostic category remain, mainly due to the following concerns: (1) Is there sufficient evidence that RBD is more than either a prodromal, residual or an associated severity marker of mood or even other existing psychopathological conditions?; (2) Is RBD sufficiently frequent and disabling in psychosocial and clinical terms in the community and clinical settings to deserve further research emphasis?; (3) To what degree are data available demonstrating consistently and sufficiently unique patterns of vulnerability and risk factors for first onset and pathogenesis of RBD?

Aims

In order to provide further research data pertaining to these critical issues focusing especially on adolescents and young adults, this paper presents findings on the prevalence, incidence, correlates and patterns of co-morbidity of RBD defined by stringent research diagnostic criteria from a large-scale epidemiological study with a total of more than 3000 respondents, who were followed over a period of almost 4 years in a total of three waves (Lieb *et al.* 2000). Unlike most other studies on RBD, it is noteworthy that the study was not specifically designed for the evaluation of RBD. However, as part of the

standardized diagnostic assessment the study included a separate diagnostic module for RBD, that was administered in only those respondents with no signs of a major depressive episode within the past 12 months. In the light of previous findings this constitutes a particular restrictive test to explore the frequency of RBD resulting in lower bound estimates in terms of prevalence and incidence, and also provides new data about RBD in a particularly young sample aged 14–24 at the outset of this study.

Specific aims of this paper are: (1) estimation of the (lower bound) prevalence for RBD along with a description of its symptoms, frequency and duration patterns in a community sample of adolescents and young adults; (2) a comparison of RBD, MDD and CD associated impairments/disability as well as other clinical correlates in this sample and to determine excess markers; and, (3) a description of 12-month and lifetime patterns of co-morbidity in RBD or CD.

METHOD

Design

The overall design of the Early Developmental Stages of Psychopathology Study (EDSP) is a prospective longitudinal design based on a representative community sample of 3021 adolescents and young adults living in the Munich area. The age range for the targeted population was chosen to address especially the early developmental stages of substance use, abuse and dependence and other mental disorders. The EDSP study consists of a baseline investigation, two follow-up investigations and an independent parent survey. Because of the focus on early developmental stages of psychopathology and substance use, only the younger cohort of adolescents, aged 14–17 at baseline, was examined in the first follow-up investigation. In the final follow-up investigation, the entire baseline sample was assessed again. Methodological aspects of this study have been described in greater detail elsewhere (Lieb *et al.* 2000).

Sample

The EDSP sample was drawn randomly from the 1994 government population registers of residents in metropolitan Munich and the surrounding counties with an expected age range for

the sampled subjects between 14 and 24 at the time of the baseline interview in 1995. As the study was designed as a longitudinal panel with special interest in early developmental stages of psychopathology, 14–15-year-olds were sampled at twice the probability of people 16–21 years of age, and 22–24-year-olds were sampled at half the probability of the 16–21-year-olds. From the total of 4809 sampled individuals, 4263 were located and determined to be eligible for the study. Sampled individuals who were not located were disproportionately older. In comparison to located subjects, subjects who could not be contacted had either moved outside the metropolitan Munich area in the time interval between their registration and the beginning of the study in 1995 (8.8%) or they could not be found with the listed address during the fieldwork period (2.4%). From the 4263 individuals a total of 3021 could be assessed at baseline (T0, response rate = 71%). Informed consent was obtained from the participants.

The first follow-up study (T1) was conducted only for subjects aged 14–17 at baseline, whereas the second follow-up study (T2) was conducted for all subjects. In the first follow-up, an average of 20 months after baseline, a total of 1228 interviews were completed (response rate = 88%). From the 3021 subjects of the baseline-study, a total of 2548 interviews were completed at the second follow-up, which was conducted an average of 42 months after baseline (response rate = 84%). There was no selective attrition due to age, gender, or geographic distribution between the baseline and second follow-up investigation. More details about the sampling and representativeness of the whole EDSP-sample along with its sociodemographic characteristics and a detailed list of reasons for non-response have been reported elsewhere (Lieb *et al.* 2000).

Diagnostic assessment

In all three waves, symptom and diagnostic assessment were based on the computer-assisted version of the Munich-Composite International Diagnostic Interview (M-CIDI) (Wittchen & Pfister, 1997). The M-CIDI is an updated version of the World Health Organization's CIDI version 1.2 (World Health Organization, 1990) incorporating questions that assess DSM-IV and ICD-10 criteria. The M-CIDI allows for

the standardized assessment of symptoms, syndromes and diagnoses of a wide range of DSM-IV substance use and mental disorders along with information about onset, duration, clinical and psychosocial severity. Links to publications on M-CIDI and further aspects of general diagnostic assessment in this study can be seen elsewhere (Lachner *et al.* 1998; Wittchen *et al.* 1998*a, b*).

At baseline, the lifetime version of the M-CIDI was used. At each of the follow-up assessments, the M-CIDI interval version, which refers to the time period of assessment from the last interview until the present, was applied. For those respondents aged 14–17 at baseline, the complete follow-up status T0–T2 is assessed from the aggregation of information obtained from the T1 and T2 interviews. For respondents aged >17 at baseline, the complete follow-up status is assessed from the second follow-up questions, which cover the time between T0 and T2.

Assessment of MDD and dysthymia

Besides threshold MDD it is possible to compute from the M-CIDI subthreshold MDD (sMDD) using the WHO-CIDI algorithm (Üstün & Sartorius, 1996). This diagnosis is assigned when respondents fall short of just one diagnostic criterion, by failing to report either the mandatory five of a total of nine DSM-IV symptoms (criterion A) or clinical significant distress or impairment (criterion C). According to DSM-IV rules, the diagnosis of dysthymia can only be made if dysthymic symptoms appeared at least 2 years prior to the first MDD episode, or if there has been a full remission of at least 2 months of MDD episode before the onset of dysthymia.

Assessment of RBD

RBD has been assessed by M-CIDI. Since the assessment of RBD in this study is crucial for the comparison to other studies, we will describe RBD evaluation in detail. The stem question was the same as for MDD episodes (depressive mood or loss of interest) except duration, which in RBD had to persist for <2 weeks. Additionally, number of brief depressive episodes during the last 12 months (or since the last interview), their average and maximal duration was evaluated. Furthermore, the presence and absence of all 35 psychopathological symptoms of depression

covered by the MDD section of the CIDI were assessed. The threshold diagnosis of RBD used in this paper followed ICD-10 research diagnostic criteria (about monthly appearance, independence of the menstruation cycle, <2 weeks duration). Subthreshold RBD was defined either reporting <8 episodes per year or falling beyond the mandatory psychopathological criteria of depression as already reported for sMDD. CD was longitudinally defined in this study as lifetime co-occurrence of RBD and MDD including subthreshold manifestations using the same procedures being mentioned above (e.g. MDD at baseline and RBD at T1 was labelled as CD, etc.).

However, two issues have to be pointed out, which in this investigation can be seen as being a restrictive test for the concept of RBD. First, RBD has not been evaluated at T0, which may lead to an underestimation of the true cumulative incidence rate of RBD. Secondly, the branching structure of M-CIDI (and most other common interviews) determines that a subject is only asked for brief depressive episodes in case of a denial of MDD stem questions. This hierarchy determines that RBD cases have only been identified within this study in the absence of MDD either at T1 or T2. Therefore, results on RBD evaluated in this study can be seen as lower bound estimates.

Statistics

To account for different sampling probabilities for the different age groups, non-contact and non-response, all measures were estimated using weighted data. For the analyses of associations between bivariate variables, logistic regressions for binary responses (odds ratio OR) were used. For quantitative outcomes (e.g. number of impaired days) negative binomial regressions were used. Associations are described by so-called incidence rate ratios (IRRs), i.e. the factor by which the mean differs from that of the comparison group. Analyses were performed using the Stata software package (StataCorp, 2001) and applying the Huber-White sandwich matrix for weighted data (Royall, 1986), including them as independent variables in the respective model controlled for sex and age of the respondents. All lifetime prevalences provided in this paper represent lifetime-to-date prevalences ($P < 0.05$ was considered as statistically significant).

Table 1. *Prevalence rates of assessed depressive disorders among study participants of three waves*

	Frequencies of depressive disorders at baseline and before (<i>N</i> = 3012)			Cumulative frequencies of depressive disorders after baseline until the last wave		
	<i>N</i>	%w	(95%CI)	<i>N</i>	%w	(95%CI)
Any depressive disorder†	467	20.3	(18.6–22.2)	549	21.3	(19.6–23.2)
– any MDD	272	12.5	(11.1–14.1)	344	13.9	(12.5–15.5)
– any sMDD	164	6.5	(5.5–7.7)	136	5.1	(4.2–6.1)
– Dysthymia	60	2.4	(1.8–3.2)	63	2.3	(1.8–3.0)
– any RBD/sRBD	NA	NA		71	2.6	(2.0–3.4)
– any RBD	NA	NA		52	1.9	(1.4–2.6)
– any sRBD	NA	NA		19	0.7	(0.4–1.2)
RBD subgroups based on course information any RBD/sRBD, never MDD/sMDD	NA	NA		48	1.6	(1.2–2.2)
– any RBD, never MDD/sMDD	NA	NA		34	1.2	(0.8–1.7)
– any sRBD, never MDD/sMDD	NA	NA		14	0.5	(0.3–0.8)
any RBD/sRBD and MDD/sMDD‡	NA	NA		23	1.0	(0.6–1.6)

MDD, Major depressive disorder; RBD, recurrent brief depressive disorder; sMDD, subthreshold MDD; sRBD, subthreshold RBD; NA, not evaluated at baseline; *N*, unweighted *N*; %w, weighted to reflect the sampling scheme; CI, confidence interval.

† Without using diagnostic hierarchies and exclusions.

‡ Combined depression.

RESULTS

Cumulative incidence of RBD and other depressive disorders

Already at baseline, depressive disorders have been highly prevalent in our sample (21.3%). The upper portion of Table 1 shows the lifetime prevalence of depressive disorders assessed at baseline and the (cumulative) incidence over the 4-year follow-up period. At baseline, 12.5% of the sample aged 14–24 reported at least one episode of MDD according to DSM-IV criteria over their lifetime; and additional 6.5% fulfilled criteria for subthreshold depression and 2.4% for dysthymia. No estimates for RBD were available for the baseline investigation.

In the follow-up period, in additional 344 and 136 cases, unaffected at baseline reported incident episodes of either threshold (13.9%) or subthreshold (5.1%) MDD, and another 63 cases fulfilled criteria for dysthymia (2.3%). At either the first or second follow-up a total of 71 subjects (2.6%) met criteria for threshold or subthreshold RBD among which the majority were threshold RBD cases (1.9%). These estimates do not take into account other diagnostic hierarchies or exclusions (schizophrenia and other psychotic disorders) for neither RBD nor MDD. However, bipolar II and I disorder were excluded.

Taking into account co-occurrences between RBD/sRBD and MDD/sMDD (lower portion

of Table 1), 1.2% (0.5%) reported RBD (sRBD) without lifetime history of MDD or sMDD and 1% reported RBD or sRBD with lifetime history of MDD or sMDD. This indicates that among all depressive disorders the proportion of RBD/sRBD is at least 12%.

In the remainder of the paper all comparisons will be based on the RBD cases as defined in the lower portion of Table 1, thus specifying whether RBD or sRBD occurred without or within (combined depression) the lifetime history of MDD/sMDD.

Gender

Controlling for age, MDD and dysthymia, but not RBD revealed significant differences with regard to sex (Table 2). Whereas there is a significant 2:1 preponderance of females in the former, there is a slight, yet not significant preponderance of males in RBD except CD.

Profile of depressive symptoms in RBD, MDD and their subthreshold manifestations

Table 3 compares the frequency of depressive symptoms in five mutually exclusive groups of depression. Highest overall symptom counts were found for CD (mean 7.3, 95%CI 6.6–7.9) followed by the MDD group (mean 6.2, 95%CI 6.0–6.4). The sRBD group (mean 2.1, 95%CI 1.9–2.3) revealed the lowest mean number of

Table 2. Comparison of gender differences in depressive disorders

	%w		OR	(95%CI)
	Male	Female		
Any RBD/sRBD, never MDD/sMDD	2.0	1.3	0.6	(0.3–1.2)
Any RBD, never MDD/sMDD	1.4	1.0	0.7	(0.3–1.5)
Any sRBD, never MDD/sMDD	0.6	0.3	0.5	(0.2–1.6)
Any RBD/sRBD and MDD/sMDD†	0.8	1.1	1.3	(0.5–3.4)
Any MDD, never RBD/sRBD	9.2	16.9	2.0*	(1.5–2.6)
Any sMDD, never RBD/sRBD	3.7	6.1	1.7*	(1.1–2.6)
Dysthymia	1.7	3.0	1.8*	(1.0–3.2)

%w, Weighted to reflect the sampling scheme, OR, odds ratio controlled for age; CI, confidence interval; MDD, major depressive disorder; RBD, recurrent brief depressive disorder; sMDD, subthreshold MDD; sRBD, subthreshold RBD.

† Combined depression.

* $P < 0.05$.

symptoms as compared to RBD (mean 4.0, 95%CI 3.7–4.4) and sMDD cases (mean 4.5, 95%CI 4.4–4.8). Comparing the confidence intervals of the means, RBD cases did not differ from sMDD cases regarding to the overall symptom count.

A comparison between RBD and MDD cases revealed that MDD cases reported a significantly higher frequency of depressed mood (OR 3.1, 95%CI 4.2–25.1), loss of interest or pleasure (OR 3.1, 95%CI 1.4–6.7), change in appetite (OR 3.2, 95%CI 1.4–7.3), change in psychomotor activity (OR 3.7, 95%CI 1.3–10.7), loss of confidence/self-esteem, feelings of self-reproach/guilt (OR 2.5, 95%CI 1.1–5.4), diminished ability to think/concentrate (OR 9.6, 95%CI 4.0–23.4) and recurrent thoughts of death/suicide, or suicidal behaviour (OR 9.6, 95%CI 3.5–26.2). No significant differences have been found concerning decreased energy or increased fatigability and sleep disturbance of any type. Interestingly, only sleep disturbances had a tendency towards a higher frequency in RBD. Nevertheless, a comparison between CD and MDD cases showed that CD cases reported significantly more frequently loss of interest or pleasure (OR 5.1, 95%CI 1.4–18.0), decreased energy or increased fatigability (OR 3.4, 95%CI 1.2–12.8), loss of confidence/self-esteem, feelings of self-reproach/guilt (OR 5.6, 95%CI 1.2–25.0). In contrast, CD cases reported significantly less frequently a diminished ability to think/concentrate (OR 0.2, 95%CI 0.1–0.7) than MDD

cases. However, no significant difference has been found in CD cases as compared to RBD cases concerning this symptom.

Focusing on the comparison of the three groups exhibiting recurrent brief depressive episodes (RBD, sRBD, CD), a similar high number of episodes (13.4–15.9) with a similar average number of days being affected during any 12-month period (38.5 to 48.5) has been reported. CD cases revealed the highest values in both comparisons. There is a clear preponderance of typical brief depressive episodes with an average duration of 4.3 days in the CD, 4.1 days in the RBD and 4.6 in the sRBD group.

A comparison of clinical correlates of brief and major depressive episodes

Compared to cases with no MDD/RBD all groups, except for sRBD, revealed a significantly increased level of current subjective complaints present at T1 or T2.

In comparison to cases without MDD and RBD all investigated depression groups of RBD (OR 3.2, 95%CI 1.2–8.6), sMDD (OR 2.7, 95%CI 1.5–4.8), MDD (OR 4.7, 95%CI 3.3–6.7) and CD (OR 4.2, 95%CI 1.5–12.3) reported significant higher rates of impairment or disability at T2 with the exception of sRBD. However, MDD cases did not significantly differ from RBD and CD cases with respect to impairment or disability at T2. Similarly, disabled or impaired days within the last month at T2 among impaired between investigated depression groups of sMDD (IRR 2.2, 95%CI 1.4–3.4), MDD (IRR 3.7, 95%CI 2.2–6.2) and CD (IRR 4.5, 95%CI 1.5–13.0) showed a significantly increased number of impaired/disabled days with the exception of sRBD (IRR 0.9, 95%CI 0.2–4.5) and RBD (IRR 1.1, 95%CI 0.3–4.0) as compared to subjects without MDD and RBD. Furthermore, MDD subjects did not differ significantly from CD or RBD with respect to the number of impaired/disabled days.

With regard to mental health treatment all groups – except for sRBD – also had a similar proportion of cases reporting a mental health treatment over the observation period. RBD (OR 4.3, 95%CI 2.0–9.4), sMDD (OR 4.6, 95%CI 2.7–8.0), MDD (OR 3.9, 95%CI 2.9–5.3) and CD (OR 4.7, 95%CI 1.8–12.5) reported higher rates of treatment seeking in comparison to subjects without MDD and RBD.

Table 3. *Depression symptom profiles of studied groups*

Symptoms	sRBD (N = 14)		RBD (N = 34)		sMDD (N = 136)		MDD (N = 344)		CD (N = 23)	
	N	%w	N	%w	N	%w	N	%w	N	%w
Depressed mood	3	18.7	18	55.9	107	81.2	302	92.4	22	98.0
Loss of interest or pleasure	4	32.6	16	39.8	46	37.4	216	66.1	20	90.9
Change in appetite	2	11.1	10	33.4	57	39.6	207	64.0	17	80.8
Sleep disturbance of any type	9	68.7	29	90.4	91	68.0	274	85.0	23	100.0
Change in psychomotor activity	0	0.0	5	10.6	31	21.5	90	27.6	7	35.6
Decreased energy or increased fatigability	3	26.0	17	54.0	65	50.1	213	66.0	19	88.2
Loss of confidence/self-esteem, feelings of self-reproach/guilt	3	17.5	16	45.1	65	51.9	218	67.4	21	91.9
Diminished ability to think/concentrate	5	29.9	20	55.8	106	79.7	295	90.5	16	71.1
Recurrent thoughts of death/suicide, or suicidal behaviour	1	3.5	6	16.7	48	31.7	207	59.8	16	69.4
	Mean	(S.E.)	Mean	(S.E.)	Mean	(S.E.)	Mean	(S.E.)	Mean	(S.E.)
Overall depression symptom count	2.1	(0.1)	4.0	(0.2)	4.6	(0.1)	6.2	(0.1)	7.3	(0.3)

MDD, Major depressive disorder; RBD, recurrent brief depressive disorder; sMDD, subthreshold MDD; sRBD, subthreshold RBD; CD, combined depression; N, unweighted N; %w, weighted to reflect the sampling scheme; S.E., standard error.

Table 4. *Clinical correlates of studied depression groups*

	sRBD		RBD		sMDD		MDD		CD	
	N	%w	N	%w	N	%w	N	%w	N	%w
Impaired/disabled at T2	2	7.4	6	18.0	20	14.4	74	22.5	6	21.2
Treatment	0	0.0	12	38.7	35	29	124	38.7	10	42.5
Suicidal ideation	1	4.0	10	28.9	29	17	131	37.2	7	27.8
Suicide attempts	0	0.0	3	7.8	6	4	41	11.9	0	0.0
	Mean	(S.E.)	Mean	(S.E.)	Mean	(S.E.)	Mean	(S.E.)	Mean	(S.E.)
SCL-90 total score	0.3	0.1	0.4	0.1	0.3	0.1	0.4	0.0	0.4	0.1
Impaired/disabled days (T2)†	1.2	0.2	2.0	0.9	2.8	0.3	4.6	1.0	5.1	2.0

MDD, Major depressive disorder; RBD, recurrent brief depressive disorder; sMDD, subthreshold MDD; sRBD, subthreshold RBD; CD, combined depression; N, unweighted N; %w, weighted to reflect the sampling scheme; S.E., standard error.

† Among impaired during the last month.

All investigated groups of RBD (OR 3.6, 95%CI 1.6–8.1), sMDD (OR 3.5, 95%CI 2.0–6.2), MDD (OR 5.9, 95%CI 4.3–8.0) and CD (OR 3.7, 95%CI 1.4–9.8) except sRBD were significantly more likely than subjects without RBD and MDD to report suicidal ideation. Suicide attempts have been reported in all groups except sRBD and CD (Table 4). Suicide attempts occurred significantly more often in subjects with MDD (OR 6.4, 95%CI 3.5–10.2), sMDD (OR 26.6, 95%CI 4.8–147.6) and RBD (OR 4.1, 95%CI 1.1–15.9) than in subjects without MDD and RBD. About 10% of RBD and MDD subjects reported suicide attempts until T2 (Table 4). However, missing reports of suicidal attempts in the CD group might be attributable to the small sample size and the CD definition used in this paper including subthreshold cases.

A comparison of the Symptom Check List-90 (SCL-90) values evaluating psychiatric symptoms in the last week between subjects not affected with MDD and RBD and investigated depression groups revealed increased values in subjects with RBD (IRR 0.7, 95%CI 0.3–1.1), sMDD (IRR 0.5, 95%CI 0.3–0.7), MDD (IRR 0.8, 95%CI 0.7–1.0), and CD (IRR 0.6, 95%CI 0.1–1.1) with the exception of sRBD (IRR 0.2, 95%CI 0.3–0.6). However, MDD subjects did not differ significantly from RBD and CD.

Patterns of co-morbidity

In terms of co-morbid conditions, Table 5 reveals that the majority of cases in the investigated depression groups have mostly several lifetime co-morbid conditions in comparison to subjects without MDD and RBD.

Table 5. *Lifetime associated major mental disorders in RBD, MDD, CD in comparison to controls without RBD/MDD*

	RBD			MDD			CD		
	%w	OR	(95%CI)	%w	OR	(95%CI)	%w	OR	(95%CI)
Any anxiety disorder	46.5	2.5*	(1.1–5.5)	61.3	3.8*	(2.9–5.0)	63.8	4.5*	(1.8–11.3)
Agoraphobia w/o panic disorder	4.4	2.9	(0.4–18.4)	9.8	5.5*	(3.0–10.1)	20.6	14.4*	(4.7–44.2)
Panic disorder†	0.0	—	—	8.9	7.2*	(3.6–14.4)	14.5	13.5*	(4.0–45.0)
Social phobia	15.8	3.2*	(1.1–8.9)	23.8	4.7*	(3.2–6.8)	11.7	2.0	(0.6–7.2)
Specific phobia	23.0	1.5	(0.6–3.7)	38.0	2.7*	(2.0–3.6)	45.0	3.8*	(1.4–10.2)
Phobia NOS	11.9	2.1	(0.6–6.6)	10.5	1.5	(1.0–2.4)	14.0	2.3	(0.6–8.4)
GAD	0.0	—	—	11.8	9.7	(5.0–19.0)	9.4	8.3*	(1.7–39.2)
OCD	0.0	—	—	4.1	5.0*	(2.1–11.9)	3.2	3.9	(0.5–31.9)
PTSD	3.7	6.7	(0.8–57.1)	7.4	11.0*	(4.8–25.3)	3.6	5.6	(0.7–45.2)
Any somatoform disorder	36.9	1.5	(0.7–3.5)	56.4	2.8*	(2.2–3.7)	37.2	1.3	(0.6–2.9)
Any affective disorder	19.0	3.7*	(1.5–9.1)	100.0	—	—	81.7	69.9*	(21.7–224.8)
Hypomania/mania	3.7	1.3	(0.3–5.7)	3.0	0.9	(0.4–1.9)	0.0	—	—
Any bipolar disorder	0.0	—	—	11.8	17.7*	(9.1–34.3)	0.0	—	—
PMDD	0.0	—	—	16.2	4.1*	(2.3–7.3)	15.9	4.1	(0.8–19.8)
Any eating disorder	5.8	2.7	(0.4–19.2)	11.8	4.0*	(2.3–6.8)	10.9	4.2*	(1.1–16.3)
Any anorexia	0.0	—	—	5.7	2.8*	(1.4–5.5)	4.1	2.2	(0.3–17.3)
Any bulimia	5.8	6.2	(0.9–43.4)	8.0	5.6*	(2.7–11.5)	10.9	9.6*	(2.2–42.4)
Any substance-related disorder	52.2	1.7	(0.8–3.7)	54.1	2.2*	(1.7–2.9)	57.2	2.3	(1.0–5.7)
Nicotine dependence	28.5	1.6	(0.7–3.5)	39.4	2.7*	(2.0–3.5)	39.0	2.6	(1.0–6.6)
Alcohol abuse	39.3	2.4*	(1.0–5.8)	24.7	1.6*	(1.2–2.2)	37.5	2.8*	(1.1–6.9)
Alcohol dependence	3.7	0.4	(0.1–1.9)	13.8	2.7*	(1.7–4.1)	11.5	1.8	(0.4–7.9)
Illegal drug abuse	1.9	0.3	(0.0–1.9)	10.2	2.5*	(1.6–4.0)	12.2	2.8	(0.9–9.4)
Illegal drug dependence	8.1	4.2	(1.0–18.3)	5.9	3.5*	(1.8–6.7)	21.2	14.4*	(3.8–54.6)

MDD, Major depressive disorder; RBD, recurrent brief depressive disorder; CD, combined depression; %w, weighted to reflect the sampling scheme interval; OR, odds ratio; CI, confidence interval; NOS, not otherwise specified; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PMDD, premenstrual dysphoric disorder.

† With or without agoraphobia.

* $P < 0.05$.

In contrast to MDD, which was associated with most major mental disorders displayed in Table 5, RBD showed a more distinct profile of co-morbid disorders. Significant 12-month co-morbidities were found for any anxiety disorder (OR 3.9, 95%CI 1.7–9.2), especially agoraphobia (OR 10.1, 95%CI 1.2–86.0) and specific phobias (OR 3.3, 95%CI 1.2–8.8). However, post-traumatic stress disorder exhibited the highest 12-month co-morbidity (OR 12.9, 95%CI 1.4–115.5). It is noteworthy that none of the RBD cases fulfilled criteria for DSM-IV 12-month or lifetime premenstrual dysphoric disorder. In contrast to MDD no 12-month associations were found for panic disorder, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, any somatoform disorder, eating disorders, any hypomania, any bipolar disorder and as well as any substance use disorder. Lifetime co-morbidities were significantly increased in RBD for any anxiety disorder, agoraphobia, social phobia and alcohol abuse (Table 5). In contrast, MDD was associated with

an increase in all major mental disorders. In the case of CD more 12-month and lifetime co-morbidities than in RBD were found as compared to subjects without MDD and RBD. In contrast to RBD, CD was associated with severe conditions like illegal drug dependence as compared to subjects without MDD and RBD during 12-months and lifetime.

Overall 14.7% of RBD cases occur with no lifetime co-morbid condition, similar to the proportion of lifetime MDD (11.3%) (Table 6). RBD exhibited a significant lower multi-morbidity in terms of lifetime (more than four associated disorders) co-morbidity than MDD (OR 3.9, 95%CI 1.1–14.4). Nevertheless, 12-month (one associated disorder) co-morbidity was significantly higher for RBD than MDD (OR 0.4, 95%CI 0.2–0.9).

Only 6.9% of CD cases had no additional lifetime diagnosis indicating a pattern of multi-morbidity. CD cases even showed a significantly higher 12-month co-morbidity for one additional associated disorder (OR 2.7, 95%CI 1.1–7.0)

Table 6. *Acute and chronic multi-morbidity in RBD, MDD, CD in comparison to controls without RBD/MDD*

	RBD			MDD			CD		
	%w	OR	(95%CI)	%w	OR	(95%CI)	%w	OR	(95%CI)
Lifetime									
0	14.7	0.3	(0.1-0.8)	11.3	0.2*	(0.1-0.3)	6.9	0.1*	(0.0-0.9)
1	35.9	1.1	(0.5-2.4)	20.7	0.5*	(0.4-0.7)	17.5	0.4	(0.1-1.2)
2	33.5	2.4*	(1.1-5.3)	29.2	1.9*	(1.4-2.6)	26.7	1.7	(0.7-4.5)
3	8.5	1.2	(0.3-4.7)	13.7	2.1*	(1.4-3.1)	33.1	6.3*	(2.2-18.3)
≥4	7.5	2.3	(0.6-8.5)	25.1	9.0*	(6.1-13.5)	15.8	5.1*	(1.8-15.0)
12-months									
0	38.6	0.3*	(0.2-0.7)	38.4	0.3*	(0.2-0.4)	27.5	0.2*	(0.1-0.6)
1	49.0	2.6*	(1.2-5.5)	28.9	1.1	(0.8-1.5)	52.2	3.0*	(1.2-7.4)
2	12.3	2.3	(0.8-6.8)	18.8	3.6*	(2.5-5.3)	13.6	2.5	(0.8-8.1)
3	0	—	—	8.6	8.4*	(4.4-16.2)	6.7	6.5*	(1.4-30.8)
≥4	0	—	—	5.4	14.8*	(5.7-38.2)	0	—	—

MDD, Major depressive disorder; RBD, recurrent brief depressive disorder; CD, combined depression; OR, odds ratio; CI, confidence interval.

* $P < 0.05$.

and a higher lifetime co-morbidity for three additional associated disorders than MDD (OR 3.1, 95%CI 1.0-9.2).

The relatively few cases in the first wave of RBD assessment do not allow for a statistical analysis of course characteristics. However, our data do not support the hypothesis that RBD is a prodromal or a residual state of MDD since only 4% of subjects with any depressive disorder had a dual diagnosis. The majority of RBD subjects developed RBD in T2 without a prodromal diagnosis of MDD, sMDD, or even sRBD at T1. Only five MDD cases developed RBD either at T1 and T2. It seems noteworthy that 13 out of 20 RBD cases have been diagnosed without any other assessed threshold or subthreshold affective disorder within all three waves.

DISCUSSION

The main aim of this paper was to re-examine the concept of RBD in a community sample of adolescents and young adults under a restrictive condition, free of any bias towards an over-estimation of this diagnosis, which seemed to be necessary due to restraints in the scientific community concerning the concept of RBD (Keller *et al.* 1995). Since this is the largest community sample ever studied in the context of RBD, we consider our findings to be a major contribution to the awareness of the scientific community towards the concept of RBD.

Recurrent brief depressive disorder

Largely consistent with other epidemiological studies our data confirm the concept of RBD as a relatively prevalent and clinically relevant affective disorder exhibiting several features being distinct from MDD. Threshold and subthreshold RBD have been found to account for at least 12% of all depressive syndromes in the community being at least as prevalent as dysthymia. However, prevalence rates for RBD are substantially lower in this study than reported in other community studies reporting prevalence rates up to 50% of all depressive cases in the community or general health care (Maier *et al.* 1994a; Weiller *et al.* 1994a,b; Altamura *et al.* 1995; Angst *et al.* 2000a, Snaith, 2000). Taking the hierarchy of CIDI-M into consideration, this is similar to other diagnostic interviews, which diagnose RBD only in the absence of MDD or its subthreshold manifestation, these prevalence rates can be taken as lower bound estimations. In order to estimate lost RBD cases in our study by the hierarchy of M-CIDI, we calculated both, hierarchical and non-hierarchical prevalence rates of the sample investigated in the Zurich Study. These results suggest that we only lost 10% (maximum 20%) of RBD cases by the diagnostic hierarchy used in our study (Angst, 2001; personal communication).

In accordance with other epidemiological studies (Maier *et al.* 1994a; Weiller *et al.* 1994a,b; Altamura *et al.* 1995; Angst, 2000a; Snaith,

2000) our data reveal a balanced sex ratio in RBD, which is significantly different from all other affective disorders exhibiting an excess of female gender, which might indicate differences in underlying sex related risk factors for this disorders. Other features of RBD, like total number of episodes and an average duration of brief depressive episodes have also been in accordance with previous published studies (Maier *et al.* 1994*a*; Weiller *et al.* 1994*a, b*; Altamura *et al.* 1995; Angst, 2000*a*). Symptom profiles or RBD have been similar to sMDD and MDD although being less pronounced in comparison to the latter. Only sleep disturbances seem to have a tendency to be even more frequent in RBD than in MDD. Clinical correlates indicated a significant impact of RBD on mental health. Help-seeking behaviour reached a degree of severity similar to MDD. Suicidal ideation and suicide attempter status, the most severe psychiatric outcome measure, have been only slightly less prevalent in RBD than in MDD in our study, which is supported by other epidemiological studies (Maier *et al.* 1994*a*; Weiller *et al.* 1994*a, b*; Altamura *et al.* 1995; Angst, 2000*a*). Together with clinical studies, which demonstrated that increased impulsiveness is responsible for the occurrence of suicidal behaviour in RBD (Montgomery *et al.* 1989; Pezawas *et al.* 2002*a*), our results underline the need for treatment in this underdiagnosed patient group.

RBD showed a more distinct pattern of co-morbidity than MDD. Furthermore, RBD seems to be a less multi-morbid condition in comparison to MDD. Anxiety disorders including PTSD were the most frequently found 12-month co-morbidities of RBD. Whereas an increased co-morbidity of anxiety disorders has been reported previously (Angst, 1994*b*), PTSD has been investigated in the context of RBD for the first time in this study and turned out as the highest associated co-morbid condition. It seems to be noteworthy that RBD lacked a lifetime association with premenstrual dysphoric disorder, which demonstrates that these disorders are not associated features. Apart from anxiety disorders alcohol abuse seemed to be the second major lifetime co-morbid condition of RBD. No association with hypomania or bipolar disorders have been found in our sample arguing against the hypothesis that RBD could be a part of the bipolar spectrum.

One major aim of the study was to investigate the hypothesis, that RBD is only an associated feature of another mental disorder and therefore might be a type of severity marker. The low number of co-morbidities and the rather low associations with co-morbid conditions found in our study reject that hypothesis. Our data, including results of prevalence, gender distribution, co-morbidity analysis and clinical correlates support the definition of RBD as a distinct disorder.

Interestingly, all co-morbid conditions associated with RBD (anxiety disorders, PTSD, alcohol abuse) and many features of RBD (depression, suicidal behaviour, impulsiveness) are thought to be associated with a malfunction of the serotonergic system (Mann *et al.* 2001). However, the first and only published controlled clinical trial (Montgomery *et al.* 1994) on the efficacy of a serotonergic agent in RBD including patients with repeated suicide attempts revealed a negative result. Recently, several case reports (Amore *et al.* 1998), one open trial (Stamenkovic *et al.* 2001) and progress in study design of RBD therapeutic trials (Pezawas *et al.* 2002*a*; Post *et al.* 1998) question this previously found negative result with serotonergic agents. However, our findings emphasize the hypothesis (Post & Weiss, 1998), that the serotonergic system might be involved in the phenomenon of RBD.

Other than threshold RBD, sRBD seems to play a minor role. Our data do not support a major clinical need for a broader definition of RBD.

Combined depression

Combined depression as defined in our study was almost as prevalent as RBD, but shared many features with MDD like a tendency towards female gender excess, and exhibited a depression symptom profile, which was even higher than in MDD for half of all assessed diagnostic symptom criteria for depression. Clinical correlates have been similar to MDD except suicide attempt rates. No suicide attempt has been observed in our CD group. This result is in contradiction to previous results indicating that CD is a high risk population for suicide attempts, which has been found by epidemiological (Angst, 1994*b*; Maier *et al.* 1994*a*) and clinical (Montgomery *et al.* 1989; Pezawas *et al.* 2002*a*) studies. Because of the low prevalence of subjects with both,

threshold RBD and MDD, and resulting problems with statistical power, we decided to include subthreshold manifestations of RBD and MDD in the definition of CD. This and the small number of observed CD cases might be attributable that our subjects did not report suicide attempts. Nevertheless, suicidal ideation has been similar to MDD indicating a clinical severe condition. CD like MDD has been found to be associated with a bundle of multi-morbidity. Interestingly, clinically more severe psychiatric disorders like drug dependence showed extremely high associations with this condition. However, apart from the suicide attempter status our data confirm results of previous studies (Angst & Merikangas, 1997) indicating that CD is a more severe condition than MDD.

This study has some limitations. First, RBD has not been assessed at baseline, which means that our findings can be seen as lower bound estimations. On the other hand this situation provided the possibility to investigate the concept of RBD in a restrictive condition free of any BIAS towards an overestimation of RBD cases. Secondly, the definition of CD included subthreshold cases for statistical reasons, which means that our CD group is less severely ill than it would be for the threshold definition. However, even using this weak definition of CD, we could confirm that CD is a more severely disordered condition than MDD. Nevertheless, further studies should define CD as threshold diagnosis in order to assess the severity of this concept properly.

Our data suggest that RBD is a prevalent clinical condition among depressive disorders being at least as prevalent as dysthymia. Furthermore, RBD is associated with significant clinical impairment sharing many features together with MDD. However, other features like gender distribution or co-morbidity patterns differ essentially from MDD. Furthermore, the lifetime co-occurrence of both, MDD and RBD indicates a severe psychiatric condition.

This work is part of the Early Developmental Stages of Psychopathology (EDSP) Study and is funded by the German Ministry of Research and Technology, project no. 01 EB 9405/6 and 01 EB 9901/6. Principal investigators are H.-U. Wittchen and R. Lieb. Current or former staff members of the EDSP group are K. von Sydow, G. Lachner, A. Perkonig, P. Schuster,

F. Gander, M. Höfler and H. Sonntag as well as E. Beloch, M. Fuetsch, E. Garczynski, A. Holly, B. Isensee, M. Mastaler, C. Nelson, H. Pfister, V. Reed, D. Türk, A. Vossen, U. Wunderlich and P. Zimmermann. Scientific advisors are J. Angst (Zurich), J. Margraf (Basel), G. Esser (Potsdam), K. Merikangas (NIMH, Bethesda) and R. Kessler (Harvard, Boston).

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