Eur Arch Psychiatry Clin Neurosci (2000) 250 : 48–52

ORIGINAL PAPER

Adam Wichniak · Dieter Riemann · Andrea Kiemen
Ulrich Voderholzer · Wojciech Jernajczyk

Comparison between eye movement latency and REM sleep parameters in major depression

Received: 23 March 1999 / Accepted: 23 November 1999

Abstract Alterations of sleep can be observed polysomnographically in approximately 90 percent of depressed patients. Most of the registered sleep abnormalities in depression also occur in other psychiatric disorders. Only some types of REM sleep alterations – short REM latency, increase of REM density and shortening of mean latency of eye movements – were reported as more specific for affective disorders.

In the present study polysomnograms of 21 medication free patients with major depressive disorder (assessed with a structured interview for DSM-III-R and Hamilton Scale) and 21 healthy controls were analysed. REM latency (LREM), REM density (RD), latencies of eye movements (LEM) and mean latency of eye movements (M-LEM) were calculated for both groups. Depressed patients (compared with healthy controls) showed increased RD (38.2% vs. 28.2%, $p < 0.0001$), shortened M-LEM (35.7 s vs. 48.3 s, $p < 0.04$) and shortening of LEM in the 1st (28.9 s vs. 48.9 s, $p < 0.007$) and 4th (27.0 s vs. 59.1 s, $p < 0.043$) REM sleep periods. LREM was not shortened significantly in depressives (78.5 min vs. 91.3 min, ns). In healthy subjects a negative correlation between M-LEM and RD was found (rho = - 0.47, $p < 0.03$).

Since in the current study depressed patients differed from healthy controls, especially concerning phasic activity during REM sleep, presented data support the essential role of REM density for the assessment of sleep in depression. As a quick and easy manner to compute measurement, M-LEM is suggested as additional parameter for the assessment of phasic activity during REM sleep.

Key words Major depression · REM sleep · REM latency · REM density · Latency of eye movement

A. Wichniak (✉) · W. Jernajczyk
Institute of Psychiatry and Neurology,
Department of Clinical Neurophysiology, Al. Sobieskiego 1/9,
02-957 Warsaw, Poland
e-mail:wichniak@mp.pw.edu.pl,
Tel.: (+48) 22 642-66-11 ex. 326,
Fax: (+48) 22 642-53-75

D. Riemann · A. Kiemen · U. Voderholzer
University of Freiburg,
Department of Psychiatry and Psychotherapy, Hauptstrasse 5,
D-79104 Freiburg, Germany

Introduction

Abnormalities of sleep pattern observed in patients with primary depression are some of the most reliable biological parameters for this disorder. Prolongation of sleep latency, increased number of awakenings, especially in the second half of the night and early in the morning, reduction of delta sleep, short REM latency and increase of REM density, especially during the first REM period, are the most common sleep disturbances in depression (Benca et al. 1992; Berger & Riemann 1993; Gillin et al. 1984; Kupfer 1976; Kupfer et al. 1978, 1980; Lauer et al. 1991; Riemann et al. 1994). Most of these sleep abnormalities however, also occur in other psychiatric disorders. Only some types of REM sleep alterations, e.g. short REM latency (Kupfer 1976) and increase of REM density (Lauer et al. 1991; Riemann et al. 1994) were described as more specific for depression. In most of the studies on the sleep of depressed patients, REM latency showed negative age dependence and became increasingly shortened with progressive age in depressed patients compared to healthy controls. REM density was unrelated to age and was heightened in depressed patients compared to that in healthy controls throughout the whole age range (Gillin et al. 1981; Lauer et al. 1991; Riemann et al. 1994). Therefore, REM density seems to be the most reliable marker for sleep in depression.

In the early 1980s two additional parameters of REM sleep: latency of eye movement (LEM) - time between the start of REM sleep period and the first eye movement in this REM period – and mean latency of eye movements (M-LEM) - mean value of the latencies of eye movements from all REM sleep periods – were proposed (Jernajczyk 1986). Since this time the usefulness of LEM and M-LEM for assessment of sleep recordings has been evaluated in

different groups of psychiatric patients, especially patients with affective disorders (Jernajczyk 1986, 1995a). Also the influence of some psychotropic drugs on M-LEM and LEMs was described (Gillin et al. 1994; Jernajczyk 1995b; Kobusiak and Jernajczyk 1990). In the initial report on M-LEM by Jernajczyk (1986) a significant shortening of M-LEM and LEM in 1st and 3rd REM sleep periods was found in bipolar depressed patients compared to healthy subjects. It is interesting to note that the difference in M-LEM between depressed patients and healthy controls in this study was higher than the difference in REM latency – the best established and described parameter for sleep in depression. Further, it was suggested that M-LEM might be a more sensitive indicator of the phasic events of REM sleep than REM density. Similar results for M-LEM and LEM were obtained in a study investigating changes of REM sleep parameters after a single dose of ipsapirone (a $5HT1_A$ receptor agonist) in healthy volunteers (Gillin et al. 1994). In the light of these reports, M-LEM seems to be a very promising parameter as an indicator of phasic activity in REM sleep to discriminate depressed patients and healthy subjects in a reliable and valid way. Since the previous observation on M-LEM were performed only in relatively small samples of patients and healthy subjects (n = 10), the aim of the present study was to confirm earlier observed changes in M-LEM and LEMs in a larger sample of depressed patients, and to compare M-LEM with REM density and REM latency.

Methods and Materials

Twenty-one randomly selected polysomnograms of patients with a major depressive disorder (15 females and 6 males) with a mean age of 38.9 ± 11.9 (range: 19-56), and twenty-one polysomnograms of healthy controls (8 females and 13 males) with a mean age of 35.6 ± 9.5 (range: 24-53) were studied. The diagnosis of depression was confirmed with the structured clinical interview for DSM-III-R, German Version (Wittchen et al. 1987). The 21-item Hamilton Rating Scale for Depression (Hamilton 1960) was used to rate the patient's mood. Patients with comorbid psychiatric disorders or suffering from significant medical disorders were excluded from the study. The depressed patients were free of any kind of psychoactive medication for a minimum of 7 days prior to the investigation. The physical health of patients and control subjects was confirmed by routine blood tests, ECG, EEG and a thorough medical examination. A personal or family history of psychiatric disorders was ruled out by a psychiatric interview in the control group. Each examined patient/control subject gave his/her informed consent prior to the investigation.

The sleep examinations were performed during two consecutive nights in the sleep laboratory of the Psychiatric Clinic of the University of Freiburg. The first night served for adaptation to the sleep laboratory conditions, the second night was considered as baseline. Sleep recordings were performed by 17 channels Nihon Koden EEG polysomnograph, from "lights out" (11:00 p.m. ± 30 min) to "lights on" (07:00 a.m.) at a paper speed of 10 mm/s. Registered parameters included EEG (C3-A2, C4-A1), EOG, surface EMG of chin and anterior tibialis muscles, ECG and respiratory parameters. The following filter settings were used: EEG: sensitivity 7 μV/mm, TC (time constant) 0.3 s, HI (high frequency filter) 70 Hz, EOG sensitivity 30 μV/mm, TC 2.0 s, HI 35 Hz; EMG: sensitivity 5 μV/mm, TC 0.03 s, HI 500 Hz. For the recording of eye movements three channels were employed. In the first two channels electrodes placed at the outer canthus of each eye were referred to the bilateral mastoid. These two channels yielded out of phase deflections for eye movements with major horizontal component but did not respond to vertical movements. The third channel recorded the vertical eye movements from electrodes placed above and below one of the eye.

Thirty-second epochs of sleep recorded during the baseline night were scored blind to diagnosis by experienced raters according to standard criteria (Rechtschaffen, Kales 1968). One of the authors (A.W.) during a one-month stay in Freiburg, measured latencies of eye movements in the analysed polysomnograms. All LEM measurements were done blind to diagnosis. Latency of eye movement is a relatively new parameter, defined as time between the start of REM period and the first eye movement in this REM period. The onset of the REM period is defined as beginning of the first epoch scored as REM according to the standard criteria (Rechtschaffen, Kales 1968). In the sleep laboratory at the Institute of Psychiatry and Neurology in Warsaw rapid eye movement is identified when the activity in both EOG-channels is greater than 25 μV and the ratio of the duration of the movement to its amplitude is less than 1 (Fig. 1). The sensitivity for EOG in our laboratory is set at 5 μV/mm and the paper speed is 15 mm/s. It means that we recognise REM, when the slope of eye movement is above 150 μV/s. On paper sleep recordings, the slope of eye movement must be over 65 degrees to fulfill these criteria. The above definitions were adjusted to the technical parameters used in sleep laboratory in Freiburg. It is particularly important for recognising rapid eye movements to observe the activity not only in one EOG channel,which helps to avoid mistakes and allows reliable measurements of LEM. Therefore we did not identify REM when we observed the activity only in the vertical EOG channel without any deflection in two other EOG channels, which measured the horizontal component of eye movements.

Mean Latency of Eye Movements was calculated as mean value of the Latencies of Eye Movements from all REM sleep periods. REM latency (LREM) was defined as the time from sleep onset (stage 2 NREM) till the first epoch of 3 minutes of REM sleep. The REM density (RD) was defined as the ratio of 3-second mini-epochs per REM period, including at least one rapid eye movement, to all of the 3-second mini-epochs per REM sleep (× 100%).

The mean values and standard deviations were calculated for all parameters. Tests for normality of continuous variables were made using the Shapiro-Wilk W test. Because of the non-Gaussian distribution of the data, the Mann-Whitney U Test was used for inferential statistics. The level of significance was set at p 0.05. Spearman Rank Order Correlation Tests were used to assess correlations between REM sleep parameters.

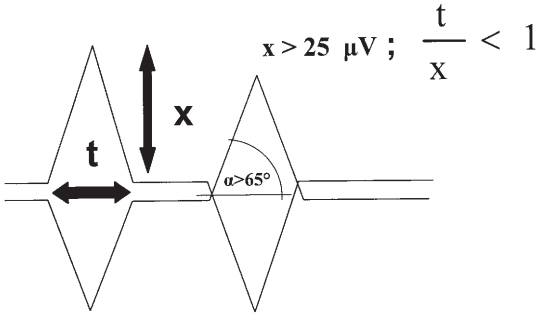

Fig. 1 Rapid eye movement is recognised if activity in EOG-channels is greater than 25 μV and the ratio of the duration of the movement to its amplitude is less than one. With a EOG sensitivity of 5 μV/mm and the paper speed of 15 mm/s, it means that the slope of REM has to be above 150 μV/s or over 65 degrees on paper recordings (x-amplitude of eye movement, t-duration of eye movement)

Table 1 REM sleep parameters for the groups of healthy controls and depressed patients (*LEM* latency of eye movement, *M-LEM* mean latency of eye movements, *LREM* REM latency, *RD* REM density)

	Healthy controls (HC)					Depressed patients (MDD)					Mann-Whitney U Test	
	Mean ± SD	Range	Median	Lower – Upper Quartile	N label	Mean ± SD	Range	Median	Lower – Upper Quartile	N label	U – values	p-level
LEM1 (s)	48.9 ± 37	6 –166	45	24 – 65	21	28.9 ± 33	4 –132	17	7.5– 29	21	115	0.007
LEM2 (s)	41.5 ± 45	8 –174	24	14 – 37	21	35.2 ± 22	6 – 80	30	17 – 50	21	201.5	ns
LEM3 (s)	53.2 ± 47	8 –168	44	13 – 78	21	35.0 ± 40	3 –138	15.5	7 – 47	18	131.5	ns
LEM4 (s)	59.1 ± 48	2 –156	48	18 – 95	17	27.0 ± 37	3 –149	12	7 – 33	15	74	0.043
LEM5 (s)	36.5 ± 31	2 –104	27	9 – 51	11	70.5 ± 77	4 –203	32	13.5–133	8	35.5	ns
M-LEM (s)	48.3 ± 20	13 – 89	50	35.5– 58	21	35.7 ± 23	7 – 91	31	17.5– 45	21	139	0.040
LREM (min)	91.3 ± 37	52 –153	72.5	62.5–123	21	78.5 ± 50	6.5–184	60	50.5–107.5	21	154	ns
RD (%)	28.2 ± 6.1	18.2– 41.2	27.8	24.2– 30.4	21	38.2 ± 8.3	24.6– 59	39.3	30.5– 42.4	21	71.5	0.0001

Results

The results of the statistical analysis are shown in Table 1. Significant differences between both groups were found in RD, M-LEM, LEM1 and LEM4. Calculation of the Mann-Whitney U Test of the above mentioned variables revealed significantly increased REM density and shortened mean latency of eye movements in patients with major depression. The depressed patients also had significantly shorter latency of eye movement in the 1st and 4th REM periods – LEM1 and LEM4. The shortening of LREM in depressed patients was not significant.

Figure 2 shows mean values, standard errors and standard deviations for M-LEM and latencies of eye movements from all REM periods for both groups.

In the group of depressed patients 2 of them (9.5%) showed lower RD than the mean value for healthy subject, and only 1 (4.7%) healthy subject had a higher RD than the mean for the depressed group. For M-LEM these results were not as marked: 4 (19%) depressed patients had longer M-LEM than the mean for controls and 6 (28.5%) controls had shorter M-LEM than the mean for depressed patients. In the group of healthy controls M-LEM negatively correlated with RD (rho = –0.47, $p < 0.03$). No other significant correlations between REM sleep parameters in healthy controls and depressed patients were found.

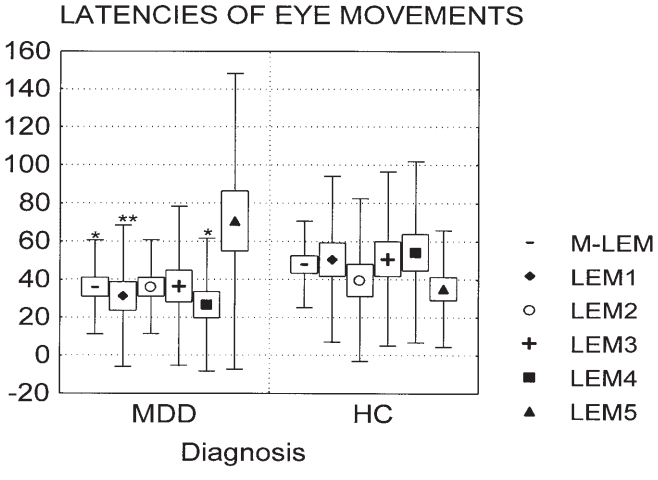

Fig. 2 Mean values, standard errors and standard deviations of mean latency of eye movements (M-LEM) and latencies of eye movements (LEM) from each REM sleep period (1–5) for the groups of depressed patients (MDD) and healthy controls (HC) (* – $p < 0.05$; ** – $p < 0.01$)

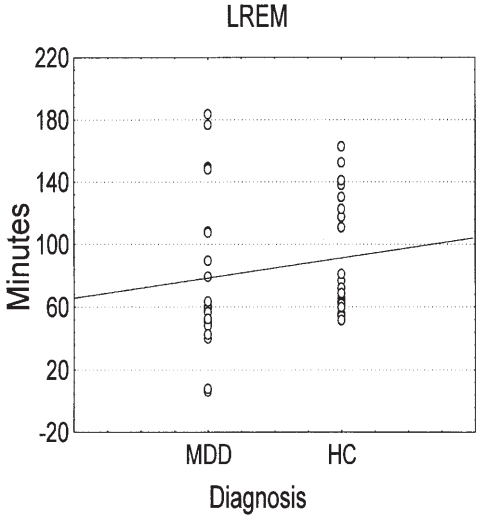

Fig. 3 REM latency (LREM) for the groups of depressed patients (MDD) and healthy controls (HC)

Discussion

Short REM latency and increase of REM density, especially during the first REM period, are described as the most common REM sleep disturbances in depressives (Benca et al. 1992; Berger & Riemann 1993; Gillin et al. 1984; Kupfer 1976; Kupfer et al. 1978, 1980; Lauer et al. 1991; Riemann et al. 1994). In our study the increase of

RD in the depressed patients showed the most pronounced difference of all examined REM sleep parameters. The shortening of LREM observed in depressed patients was not significant and, as shown in Fig. 3, it can be hardly explained by some outliers in the depressed group.

As previous studies on M-LEM the present study also showed a significant shortening of M-LEM and LEM in the 1st REM period in depressed patients. This confirms reports on M-LEM, describing M-LEM to be changed in depressed patients, even in depressed patients without marked LREM shortening. However our data disagree with studies suggesting that M-LEM is a better indicator of changes in phasic activity than RD (Jernajczyk 1986; Gillin et al. 1994), since in the present study RD was more significantly altered in depressed patients than M-LEM. Furthermore, a correlation between M-LEM and RD in the group of healthy subjects, but not in the group of depressed patients, was found. This argues that M-LEM does not assess phasic activity in the same way that RD does. In our view M-LEM should therefore rather be considered as an parameter additional to RD for estimation of phasic activity in depression. It could also, as a very quick and uncomplicated measurement, be very useful for assessment of phasic activity in situations when calculation of RD is very time-consuming, e.g., for paper sleep recordings. The importance of measurements of phasic activity in REM sleep of depressed patients is supported by reports describing RD not to be as age-dependent as LREM is. According to these studies RD seems to be a better biological marker for depression than LREM (Gillin et al. 1981; Lauer et al. 1991; Riemann et al. 1994).

In the two previous studies on M-LEM Jernajczyk (1986, 1995a) described virtually identical mean values of M-LEM - 19.4 and 19.7 s in depressed patients and 39.0 and 39.9 s in controls. In the present study the mean value of M-LEM in the group of depressed patients was 35.7 s and 48.3 s in the group of healthy controls. The reasons for longer values of M-LEM in the current study compared to previous ones are probably due to methodological differences between the laboratories. In the present study the vertical component of eye movements was registered only with one EOG channel (see methodology). As we did not recognise rapid eye movement when the activity was present only in single EOG channel, it could result in misidentifying some of the pure vertical eye movements, which did not cause any deflections in other EOG channels measuring horizontal eye movements. Feinberg et al. (1969) as well as Antrobus & Antrobus (1969) found that vertical eye movements appeared significantly earlier at the onset of REM periods than horizontal eye movements in healthy subjects. In the present study compared to the two earlier studies, the mean value of M-LEM was 16 s longer in depressed patients and only 8.5 s longer in healthy controls. Perhaps the delay between the vertical and the horizontal eye movements at the onset of the REM period is more pronounced in depressives than in healthy subjects. Maybe it could explain why in the present study we found M-LEM to be less sensitive than previously reported. The second methodological difference between present and previous studies was in paper speed, which was 10 mm/s in the current study and 15 mm/s in two earlier ones. As M-LEM is measured from the beginning of first epoch scored as REM, the change of epoch length from 20 to 30 s unquestionably influences the measurement of this parameter, because with the increase of epoch length the scoring of the start of REM period becomes less accurate. For this reason a more precise definition for the onset of LEM, than in the Rechtschaffen and Kales manual, e.g. from the last graphoelement of stage 2 or from onset of muscle tone absence, would be of great benefit.

In the other studies on the latency of eye movement it was found that M-LEM and most of LEMs were prolonged after one dose of ipsapirone as well as amitriptyline in healthy male volunteers (Gillin et al. 1994, Jernajczyk 1995a; Kobusiak and Jernajczyk 1990). The prolongation of M-LEM was also observed in depressed patients during amitriptyline treatment (Jernajczyk 1995b). Nevertheless the pathophysiological mechanisms responsible for REM sleep abnormalities in depression are not well understood. Serotonergic projections from the dorsal raphe nucleus and noradrenergic projections from locus coeruleus hyperpolarise cholinergic neurones in the pontine reticular formation and thereby inhibit REM sleep or at least the phasic events of REM sleep (Luebke et al. 1992). This serotonergic input is mediated by a $5HT1_A$ receptor. The $5HT1_A$ receptor agonist (ipsapirone) increased both M-LEM and REM latency and decreased REM% and REM density in healthy volunteers (Gillin et al. 1994). This suggests that REM sleep phenomena might be directly correlated with the serotonergic neurotransmission at the $5HT1_A$ synapse, by inhibition of cholinergic neurones. The cholinergic stimulation evoked by administration of a cholinesterase inhibitor, physostigmine (Sitaram 1976), or a muscarinic agonist, RS86 (Riemann et al. 1994), promotes REM sleep. It was proposed that the pathophysiological phenomena in sleep in depressives are consistent with the cholinergic – aminoergic imbalance hypothesis of depression (Janowsky et al. 1972) and the reciprocal - inhibition hypothesis for the regulation of NREM-REM sleep (Hobson et al. 1975, McCarley 1982). The behaviour of REM sleep parameters, especially REM density and M-LEM, described in this and previous studies in pharmacologically untreated depressed patients as well as during psychotropic treatment seems to be compatible with these hypotheses.

Acknowledgments We are indebted to Aleksandra Wierzbicka for review of the manuscript.

References

1. Antrobus JS, Antrobus JS (1969) Rapid eye movements and rapid eye movement periods. Psychophysiology 6:45–48
2. Benca RM, Obermeyer WH, Thisted RA, Gillin JC (1992) Sleep and psychiatric disorders. A meta-analysis. Arch Gen Psychiatry 49:651–668
3. Berger M & Riemann D (1993) REM sleep in depression – an overview. J Sleep Res 2:211–223

4. Feinberg I, Braun M, Koresko RL (1969) Vertical eye-movement during REM sleep: effects of age and electrode placement. Psychophysiology 5:556–561
5. Gillin JC, Duncan WC, Murphy DL, Post RM, Wehr TA, Goodwin FK, Wyatt RJ, Bunney WE (1981) Age related changes in sleep in depressed and normal subjects. Psychiatry Res 4:73–78
6. Gillin JC, Sitaram N, Wehr T et al (1984) Sleep and affective illness. In: Post RM, Ballenger JC (eds) Neurobiology of mood disorders. Williams & Wilkins, Baltimore London pp 157–189
7. Gillin JC, Jernajczyk W, Valladares-Neto DC, Golshan S, Lardon M, Stahl SM (1994) Inhibition of REM sleep by ipsapirone, a 5 HT1A agonist, in normal volunteers. Psychopharmacology 116:433–436
8. Reference deleted
9. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56
10. Hobson JA, McCarley RW, Wyzinski PW (1975) Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 189: 55–58
11. Janowsky DS, el-Yousef MK, Davis JM, Sekerke HJ (1972) A cholinergic-adrenergic hypothesis of mania and depression. Lancet 2:632–635
12. Jernajczyk W (1986) Latency of eye movement and other REM sleep parameters in bipolar depression. Biol Psychiatry 21: 465–472
13. Jernajczyk W (1995a) Latency of eye movements: the methods and applications. In: Szelenberger W and Kukwa A (eds) Sleep physiology and pathology. Elma Books, Warsaw, pp 113–115
14. Jernajczyk W (1995b) The influence of amitryptiline on pattern of REM sleep in depression. Acta Nerobiologiae Experimentalis 55 suppl. 26
15. Kobusiak M Jernajczyk W (1990) Amitryptyline and sleep pattern in healthy males follow up study. Strasbourg 20–25 May 1990
16. Kupfer DJ (1976) REM latency a psychobiologic marker for primary depressive disease. Biol Psychiatry 11:159–174
17. Kupfer DJ, Foster FG (1978) EEG sleep and depression In: Williams RL, Karacan I (eds) Sleep Disorders: Diagnosis and Treatment. New York: John Wiley and Sons
18. Kupfer DJ, Broudy D, Coble PA, Spiker DG (1980) EEG sleep and affective psychosis. J Affect Disord 2:17–25
19. Lauer C, Riemann D, Wiegand M, Berger M (1991) From early to late adulthood. Changes in EEG sleep of depressed patients and healthy volunteers. Biol Psychiatry 29: 979–993
20. Luebke JI, Green RW, Semba K, Kamondi A, McCarley RW, Reiner PB (1992) Serotonin hyperpolarizes cholinergic low-threshold burst neurons in the rat laterodorsal tegmental nucleus in vitro. Proc Natl Acad Sci USA 89:743–747
21. McCarley RW (1982) REM sleep and depression: Common neurobiological control mechanisms. Am J Psychiatry 139: 565–570
22. Rechtschaffen A, Kales A (1968) A manual of standardized terminology techniques and scorning system for sleep stages of human subjects BIS/BRI. UCLA, Los Angeles
23. Riemann D, Hohagen F, Bahro M, Berger M (1994) Sleep in depression: the influence of age, gender and diagnostic subtype on baseline sleep and the cholinergic REM induction test with RS 86. Eur Arch Psychiatry Clin Neurosci 243:279–290
24. Sitaram N, Wyatt RJ, Dawson S, Gillin JC (1976) REM sleep induction by physostigmine infusion during sleep in normal volunteers. Science 191:1281–1283
25. Wittchen HU, Zaudig M, Schromm E, et al (1987) SKID Strukturiertes Klinisches Interview für DSM-III-R. (Testversion) Weinheim: Beltz Verlag