Acta Neurobiol. Exp. 2002, 62: 243-250

Alterations in pattern of rapid eye movement activity during REM sleep in depression

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Abstract. The aim of the study was to evaluate REM sleep parameters, especially the temporal characteristics of rapid eye movement activity, in depressed patients, and to compare three different methods for scoring of REM density. The sleep of 15 nonmedicated depressed patients and 13 healthy controls was recorded during two consecutive nights. Sleep recordings were scored by raters blinded to the diagnosis. In comparison to healthy controls depressed patients showed an increased REM density and increased REM activity. Both groups differed also regarding the pattern of REM density changes between REM sleep periods (REMPs). Whereas in healthy controls REM density in the first REMP was significantly lower than in the successive REMPs, no such difference was found in depressed patients. On visual inspection we failed to find any significant differences in the time course of REM activity within the first REMP in depressed patients. All applied methods for scoring of REM density distinguished depressed patients from healthy controls with comparable accuracy.

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Key words: depression, REM sleep, REM density, REM latency, rapid eye movements

INTRODUCTION

Sleep disturbances are one of the most common symptoms encountered in depression and are part of the diagnostic criteria for this illness (DSM-IV, American Psychiatric Association 1994). Depressed patients complain about disturbed, light and unrestorative sleep and this is reflected in abnormalities of the polysomnographically verified sleep pattern that can be found in approximately 90% of patients (Mendelson et al. 1977).

The high prevalence of sleep pattern abnormalities in depressed subjects has raised the question as to whether they could serve as biological markers for this disorder. Whereas disturbances of sleep continuity and decrease in slow wave sleep are present virtually in every psychopathological condition, changes in REM sleep, especially short REM latency and increased REM density, seem to be somehow characteristic for depression (Foster et al. 1976, Kupfer 1976, Akiskal et al. 1982, Feinberg et al. 1982, Riemann et al. 1994). Kupfer showed that REM sleep disturbances, particularly short REM latency, can even be used to distinguish primary/endogenous depression from secondary forms (Kupfer 1976). However, these initial findings were not fully confirmed by more recent studies, and some forms of REM sleep abnormalities have been reported also in other psychopathological conditions, e.g., schizophrenia, eating disorders, obsessive-compulsive disorder and borderline personality disorders (Benca et al. 1992).

Despite its lack of specificity for depression, REM sleep parameters, especially REM density, recently received renewed attention as a biological parameter of interest in psychiatry. Increased REM density was shown, for example, to discriminate depression from beginning dementia in elderly patients (Reynolds et al. 1988), to predict depression in high-risk subjects (Battaglia et al. 1999) and to be associated with poor treatment response and poor longitudinal clinical course in depressed patients and patients with psychiatric disorders showing high comorbidity with depression (Keshavan et al. 1994, Rao et al. 1996, Thase et al. 1997a, Clark et al. 1998, Clark et al. 2000).

Furthermore, recent studies using discriminant analyses showed that a combination of multiple sleep parameters describes more reliably the neurobiological abnormality of the sleep profile in depressed patients than REM latency or REM density alone, and therefore may be clinically more relevant (Thase et al. 1997b).

Based on these previous studies showing the relevance of REM density as a biological parameter in psychiatric patients we performed a more detailed analysis of rapid eye movement activity (REM activity) in depressed patients and compared them with healthy controls. As there has been a number of studies published until now showing that REM density is increased in depressed patients we were especially interested in the temporal distribution of REM activity between successive REM sleep periods and within the first REM sleep period, which seems to play a special role in the sleep structure in depression. Furthermore, we concentrated on methodological aspects; we used for calculation of REM density three different methods to control if different methods of calculating REM density can yield substantial discrepancies and can explain some conflicting results in the literature. After a detailed description of REM sleep we performed a discriminant analysis to look for REM sleep parameters that best distinguish depressed patients from healthy controls.

METHODS

Subjects

The analysis was performed based on data from sleep recordings of 15 depressed patients (7 females, 8 males, mean age 41.6 ± 10.0) and 13 healthy controls (7 females, 6 males, mean age 42.3 ± 9.9).

The depressed patients were recruited from the inpatients of the Psychiatric Clinics of the Institute of Psychiatry and Neurology in Warsaw. The diagnosis of depression was confirmed with the structured clinical interview for DSM-IV categories Major Depression (n= 3) and Bipolar Affective Disorder type I (n = 12). Depressive symptoms were assessed by applying the 17-item Hamilton Depression Rating Scale and Beck Depression Inventory. All patients had HDRS score of > 14. The mean score on the Hamilton scale was 20.6 ± 4.7, on the Beck scale 24.9 ± 5.7. The mean age of onset of the disorder was 29.7 ± 8.9 years and the mean number of episodes till time of the investigation 6.7 ± 3.7. The patients were free of any kind of psychoactive medication for a minimum of two weeks prior to the investigation. None of the patients had been previously treated with fluoxetine, irreversible MAO-inhibitors or long half--life benzodiazepines in which case a wash-out period of at least four weeks is necessary. Before their inclusion into the study the depressed patients and healthy

controls were carefully interviewed and examined to rule out any somatic diseases. Waking EEG examinations were performed to exclude abnormal EEG activity. A personal or family history of psychiatric disorders in the healthy controls and comorbid psychiatric disorders in depressed patients were ruled out by a psychiatric interview performed by an experienced psychiatrist. As all recruited depressed patients were inpatients, their sleep habits were regularized prior to sleep examination. In particular, they were not allowed to take naps during daytime. Participation in the study was voluntary and informed consent was obtained from each examined patient/control subject prior to the examination.

Sleep recordings

Sleep was recorded during two consecutive nights in the sleep laboratory. The first night served for adaptation to sleep laboratory conditions. Data from the second night were used for analysis. Sleep recordings were performed with a 16 channel Medelec-polygraph with continuous EEG, electrooculography (EOG) and submental electromyography (EMG). The EOG consisted of two electrodes placed at the outer canthi of the eyes, left electrode slightly above and right electrode slightly below the horizontal plane, referred to the same mastoid (LOC/A1, ROC/A1). The EEG was recorded from left and right central electrodes, according to 10-20 international system, referred to contralateral mastoids (C3/A2, C4/A1). EMG was recorded from 2 chin surface electrodes. The following set of technical parameters was used: paper speed 15 mm/sec, sensitivity for EEG and EOG 5 μV/mm, for EMG 2 μV/mm, time constant for EEG and EOG 0.3 s, for EMG 0.1 s, high frequency filters for EEG and EOG 30 Hz, for EMG 70 Hz. The recording duration was scheduled for 8 hours from "light out" at about 10.30 p.m. to "light on" at about 6.30 a.m.

After recording, sleep recordings were scored by experienced raters blinded to clinical diagnosis in 20-s epochs according to standard criteria (Rechtschaffen and Kales 1968).

The following REM sleep parameters were calculated:

1. Duration of each REM sleep period and total duration of REM sleep. REM sleep period (REMP) was defined as not less than three consecutive minutes of REM sleep, with not less than 15 min of NREM sleep, including intervening awakening, subtending REM sleep periods (REMPs).
2. REM latency, as time from onset of sleep, defined as the first occurrence of stage 2 NREM sleep, to the first REMP.
3. Number of REMPs.
4. REM efficiency for each REMP and whole REM sleep expressed as percentage calculated by dividing the actual minutes of REM sleep time in REMP by the total duration of the REMP.
5. Latency of eye movement for each REMP, as time between the start of REMP to the first eye movement in this REMP (Jernajczyk 1986).
6. Mean latency of eye movements (MLEM), as the mean value of all latencies of eye movements.
7. Number of rapid eye movements in each REMP and number of rapid eye movements for whole REM sleep (REM activity).
8. REM density in each REMP and REM density for whole REM sleep. For calculation of REM density three independent methods were used. In method A REM density was expressed as a ratio of 2 s mini-epochs per REMP including at least one rapid eye movement to all of 2 s mini-epochs per REMP x 100%. In method B REM density was calculated on a scale of 0-4 points, based on the duration of rapid eye movement activity. No point was given if no eye movements per 20 s - epoch of REM sleep occurred, 1, 2, 3, 4 points if the duration of eye movement activity was, respectively, below 25 %, between 25% and 50%, between 50% and 75% and above 75% of epoch length. In method C REM density was expressed as the number of eye movements per minute of REM sleep. Scoring of single eye movements was also used to examine the time course of REM activity within the first REMP in both investigated groups. These three scoring methods of REM density were chosen to assess different aspects of REM activity. Whereas method B is sensitive to the time duration of rapid eye movements, method C is sensitive to the number of rapid eye movements and method A combines these two aspects.

Rapid eye movement was recognized when the activity in both EOG channels was greater than 25 μV and the slope of eye movement was over 65 degrees. For the set of technical parameters that was used, it meant that the slope of eye movement had to be above 150 μV/s. All parameters were calculated manually; no computer based automatic analysis was used.

Statistics

Mean values and standard deviations were calculated for all parameters. Nonparametric Mann-Whitney U

Table I

REM sleep parameters for depressed patients (n = 15) and healthy controls (n = 13)

	Depressed patients		Healthy controls		Mann-Whitney U Test	
	mean ± SD	range	mean ± SD	range	U-value	$P<$
REM latency (min)	77.6 ± 45.6	5.3 - 169.0	94.3 ± 35.4	51.0 - 144.3	70	ns
MLEM (s)	24.7 ± 18.6	6.3 - 68.4	36.5 ± 26.9	6.7 - 78.3	73.5	ns
REM efficiency (%)	85.0 ± 9.7	69.5 - 98.8	89.1 ± 5.8	77.6 - 98.4	74	ns
REM activity (amount)	1,073 ± 682	131 - 2,824	595 ± 220	218 - 973	54	0.05
RD A (%)	22.4 ± 8.8	9.2 - 49.1	14.2 ± 3.8	7.1 - 19.3	26	0.005
RD B (points)	2.6 ± 0.9	1.3 - 5.4	1.8 ± 0.4	1.1 - 2.3	30	0.005
RD C (amount/min)	12.1 ± 5.8	4.7 - 29.6	6.8 ± 2.1	2.8 - 9.8	27	0.005

MLEM, Mean Latency of Eye Movements; RD, REM density, method A, B, C; ns, not significant.

Test and Wilcoxon Matched Pairs Test were used for inferential statistics. The level of significance was set at $P<0.05$ two-tailed.

RESULTS

Depressed patients compared to healthy controls showed significant alterations in REM density and in REM activity (see Table I). The depressed patients had evidence of increased REM density in the first and the third REMPs, and in whole REM sleep, and an altered pattern of REM density changes between successive REMPs (see Fig. 1).

Whereas in depressed patients the first REMP did not differ in REM density from the successive REMPs and from the mean value for the whole night, in healthy controls REM density in the first REMP was significantly lower than in the successive REMPs. It was also lower than the mean value for the whole night. All the methods for calculating REM density were able to distinguish the depressed patients from healthy controls with comparable accuracy, and had strong reciprocal correlations (method A to method B $r = 0.97$; method A to method C $r = 0.92$, method B to method C $r = 0.92$; $P<0.0001$ in depressed patients and $r = 0.91$, $r = 0.93$, $r = 0.87$; $P<0.0001$ respectively in healthy controls; Spearman Rank Order Correlations Test).

Similarly to REM density also the REM activity in the first (214.7 ± 120.4 vs. 94.2 ± 74.9; $P<0.005$), third (349.2 ± 188.1 vs. 129.3 ± 82.1; $P<0.005$) REMPs and

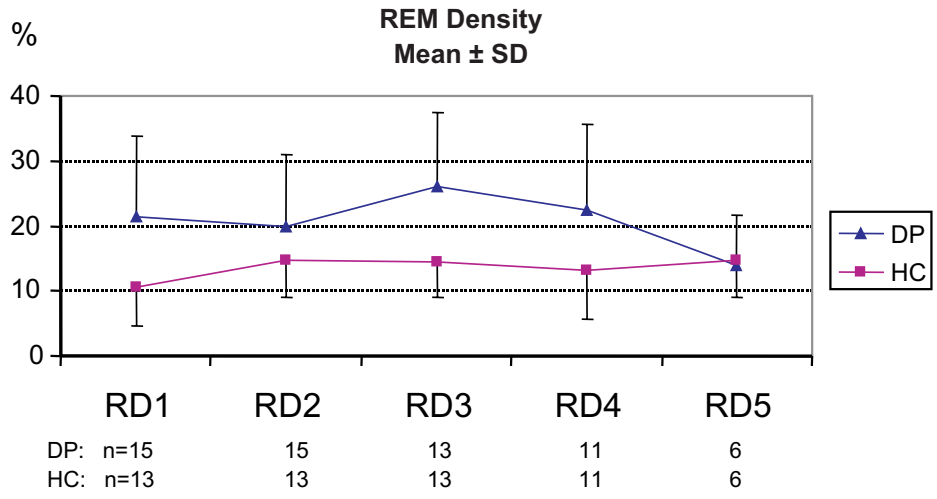

Fig. 1. Depressed patients (DP) showed increased REM density (RD) in the first ($P<0.005$) and third ($P<0.005$) REMPs and for the whole REM sleep ($P<0.005$). In healthy controls (HC) REM density in the first REMP was lower than in the successive REMPs (RD1 to RD2 $P<0.06$; RD1 to RD3 $P<0.05$; RD1 to RD4 $P<0.05$; RD1 to RD5 $P<0.05$) and than the mean value for the whole REM sleep ($P<0.05$). No such difference was found in depressed patients.

in the whole REM sleep (see Table I) was increased in depressed patients.

Within the first REMP the depressed patients displayed increased eye movement activity over the whole period length. However, no differences were found in the pattern of occurrence of REM bursts or single rapid eye movements. The latency from onset of the first REMP to the first eye movement and to the maximum of REM activity was shorter in depressed patients, but did not reach the level of significance.

Among tonic REM sleep parameters only REM sleep efficiency was decreased in the first REMP in depressed patients (92.9 ± 6.9 vs. 98.2 ± 3.1; $P<0.05$). However, for the whole REM sleep the difference in REM efficiency was not significant (see Table I). In both groups REM efficiency was the highest in the first REMP and lower in REMPs in the second part of the night.

No significant differences in MLEM, REM sleep duration and number of REMPs were found. REM latency was shortened in depressed patients, but this shortening was not significant (see Fig. 2). Sleep-onset REM period (REM latency< 15 min) was documented in one depressed patient.

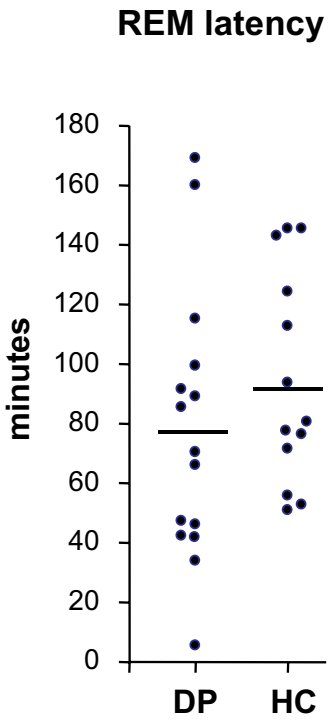

Fig. 2. REM latency for depressed patients (DP) and healthy controls (HC). Lines represent mean values.

After including examined REM sleep parameters in discriminant function analysis the combination of three parameters, REM density, REM efficiency in the first REMP and REM latency, was found as the best in identifying both groups. It correctly identified 13 of 15 depressed patients and 12 of 13 healthy controls, with overall accuracy rate of 89% ($P<0.005$). This was better than for any single REM sleep parameter (e.g., REM density – 75%, $P<0.005$; REM latency – 60%, not significant; REM efficiency in the first REMP – 64%, $P<0.05$).

DISCUSSION

In the present study we found statistically significant differences between depressed patients and healthy controls particularly in phasic REM sleep parameters. These results are in agreement with previous studies reporting REM density and REM activity as markedly increased in depressed patients, even in those without significant shortening of REM latency (Lauer et al. 1991, Riemann et al. 1994, Wichniak et al. 2000). In contrast to REM latency, the first sleep parameter found to be altered in depressed patients (Kupfer 1976), REM density is not age-dependent and is less influenced by disturbances of sleep continuity, a very common finding in psychiatric disorders (Gillin et al. 1981, Lauer et al. 1991, Riemann et al. 1994). The prolongation of REM latency due to increased nocturnal awakenings in some depressed patients makes this measure frequently unreliable. This was the case in two depressed patients in the present study with REM latency > 160 min, and explains why the observed shortening of REM latency in the group of depressed patients did not reach a statistically significant level.

In the present study we looked not only at the amount, but also for the temporal distribution, of REM activity. We found altered dynamics of REM density between successive REM periods in depressed patients. Whereas in healthy subjects REM density is low at the beginning of the night, then progressively increasing in successive REMPs (Aserinsky 1969, Takahashi and Atsumi 1997), depressed patients display already in the first REMP REM density at a level similar to that of the second half of the night (McPartland et al. 1978). Contrary to our expectations we did not find in depressed patients an altered time course of REM activity within the first REMP. However, as we analyzed REM activity based only on visual inspection, our results do not rule out that other differences in dynamics of REM activity exist in

depressed patients that could be detected with the use of more precise, computer based analyzers of REM activity, e.g., as described by Takahashi and Atsumi (1997). The detailed dynamic description of REM activity in depressed patients might reveal more state dependent and more specific alterations for depression.

A considerable problem in studies on REM density is that different calculating methods of REM density are used. This raises the question of how the reported data should be compared. In the present study we calculated REM density using three different widely applied methods. In this way we were able to determine if these different methods for calculating of REM density can yield substantial discrepancies. Our results do not support such an assumption, since all three methods significantly distinguished healthy controls and depressed patients and showed strong reciprocal correlations. As a source of possible discrepancies between studies in scoring of REM density there cannot, however, be denied the methodological differences resulting from placing of EOG electrodes, setting of technical parameters, and probably most importantly differences in definition of what is classified as rapid eye movement. In previous reports on REM density in healthy controls the reported number of rapid eye movements differed broadly from 4.2 to 24.6 per minute due to methodological differences (Takahashi and Atsumi 1997). The standardization of EOG registration procedures and scoring of REM density between sleep research centers would therefore be of great benefit.

Due to limitations in terms of specificity of single sleep parameters for depression it was proposed to combine different sleep variables to increase their specificity for depression. Thase and colleagues (Thase et al. 1997b) suggested REM latency, sleep efficiency and REM density as the most contributing variables. This combination proved to discriminate between depressed patients and healthy controls with a good test-retest reliability. In the present study we found also that not a single REM sleep parameter, but rather the combination of REM latency, REM density and REM efficiency in the first REM sleep period discriminated best between depressed patients and healthy controls. This supports earlier observations that combination of parameters describing disinhibition of REM sleep and disturbed sleep continuity well characterizes the sleep profile of depressed patients.

The critical question to be addressed is how increased phasic REM activity is related to the pathophysiology of depression at the neurobiological level. In a model of NREM-REM sleep regulation postulated by Hobson and McCarley (Hobson et al. 1975, McCarley 1982) cholinergic neurons in the brainstem played the dominant role in promoting and maintaining REM sleep, whereas brainstem noradrenergic and serotoninergic systems suppressed REM sleep. Although this model was primarily generated to account for short REM latency in depressed patients, subsequent studies showed that also phasic REM activity – rapid eye movements and pontine geniculate occipital (PGO) spikes - is regulated by the same mechanisms (Luebke et al. 1992, Gillin et al. 1996). Interestingly, a similar reciprocal balance between adrenergic and cholinergic systems was earlier hypothesized by Janowsky and colleagues as playing the major role in the development of mania or depression (Janowsky et al. 1972). Therefore, it was assumed that the neurobiological mechanisms controlling REM sleep and those responsible for depressive phenomena are parallel. However, although monoamine deficiency hypothesis of depression enjoyed considerable support, since it attempts to provide a pathophysiologic explanation of the action of antidepressants, it does not fully explain the pathophysiology of depression, e.g., why it takes several weeks before antidepressants become effective, whereas monoaminergic effect occurs within hours. Therefore, some concurrent hypotheses were recently proposed, e.g., the corticosteroid receptor hypothesis of depression (Holsboer 2000). But, it has to be stated that the exact pathophysiology of depression remains still unknown and requires further research (Nestler et al. 2002).

Furthermore, the advent of trazodone and nefazodone, two antidepressants not inhibiting REM sleep, led to a reevaluation of the earlier assumptions that the disinhibition of REM sleep is directly connected to pathophysiology of depression and suppression of REM sleep is necessary for successful antidepressant effect (Armitage et al. 1994). However, in our opinion this fact should not stop further studies on REM sleep in depression, as depression is a heterogeneous disorder and its pathophysiology is also influenced by environmental stress factors and social strengthening mechanisms. Therefore, the absence of a direct correlation between any biological factor and clinical symptoms of depression should not be disappointing as long as a given biological parameter can be found in a majority of depressed patients, and seems to be related to biological vulnerability to depression, as it is the case for REM sleep abnormalities (Lauer et al. 1995). A lack of speci-

ficity for depression should also not discredit REM sleep parameters since a modern psychopathology-oriented classification of psychiatric disorders may not be relevant to underlying biological mechanisms and common biological factors may exist in different psychiatric disorders. This is one of the explanations of the beneficial action of antidepressants in panic, obsessive- compulsive and anxiety disorders and the high comorbidity between these disorders and depression.

Recent advances in molecular biology enable researchers to investigate directly the genomics and proteomics of depression. However, to use such modern research methods in psychiatry it is necessary that psychiatrists would be able to characterize in detail the phenotype of their patients. Whereas the depressive symptomatology can be reliably evaluated with several self- and clinician administered rating scales the assessment of neurobiological abnormalities in depressed patients remains difficult. As sleep architecture is one of the most individual stable biological parameters and REM sleep abnormalities belong to the most replicated biological abnormalities in depression, it could be one of the possibilities to address more accurately the phenotypes of depressives.

CONCLUSIONS

The increase in REM density in depression is accompanied by alterations in the pattern of REM density changes between REM sleep periods. The different calculating methods of REM density do not yield substantial discrepancies if the definition of rapid eye movement and technical parameters are kept the same.

ACKNOWLEDGEMENTS

We are grateful to Dr Sean P. Morrissey for helpful comments and suggestions and to Eugenia Szatkowska, Krystyna Czasak and Iwona Musińska for excellent assistance with the sleep recordings.

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Received 2 January 2002, accepted 19 September 2002