Electroencephalography and clinical Neurophysiology, 1987, 67: 499–507
Elsevier Scientific Publishers Ireland, Ltd.

EEG 01965

Clinical Section

Rapid eye movements, muscle twitches and sawtooth waves in the sleep of narcoleptic patients and controls [1]

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(Accepted for publication: 4 March, 1987)

Summary Seventeen unmedicated patients with narcolepsy-cataplexy and 17 age- and sex-matched controls were recorded polygraphically for 3 consecutive nights. Rapid eye movements (REMs), m. mentalis twitches and sawtooth waves in the EEG were visually scored. REM and twitch densities during REM sleep were significantly higher in the patients than in the controls. The distribution pattern of REMs and twitches was altered in the patients: twitch density peaked in the first REM period and density of REMs showed an even distribution across all the REM periods of the night. In the controls both REM and twitch density increased from the first to the second REM period. We therefore assume that in the narcoleptics phasic activity of REM sleep is disinhibited. Densities of REMs, twitches and sawtooth waves did not correlate with one another in patients and controls. They appear to be independently regulated. The REM periods of the patients contained 3 times as many waking epochs as those of the controls. This suggests that in narcolepsy the transition REM/waking is selectively facilitated. The REM/NREM ratio of twitch and sawtooth wave densities was the same in patients and controls.

Key words: Narcolepsy; Phasic activity; REM twitches; Sawtooth waves; REM density; REM fragmentation

REM sleep is characterized by a desynchronized EEG pattern along with suppressed or greatly reduced tone in most muscle groups, and by bursts of rapid eye movements (REMs). Besides the REMs, a variety of other discontinuous, phasic phenomena occurs, mainly during REM sleep although most of them can also be observed during NREM sleep at a lower rate. Phasic discharges, which actively overcome the tonic motor inhibition of REM sleep (Chase and Morales 1983; Glenn and Dement 1985), are present in many muscle groups; the bursts of activity seen in the chin EMG are but one example. Another phasic phenomenon of REM sleep, which can be observed in the EEG, is the sawtooth waves (STW, Roth 1980). They are distinct trains of regular EEG waves with a triangular form and tend to occur within a few seconds before the onset of REM bursts (Berger et al. 1962).

It has been suggested that the tonic and the various phasic components of REM sleep are generated by separate sets of neurones (PS subsystems) which are under the direct control of PS-on and PS-off neurones. These in turn are under the control of other neural, and possibly humoral factors (Sakai 1985). The putative effectors for some of the phasic REM sleep phenomena have been localized in the brain-stem (Hobson et al. 1986).

In man a direct investigation of these systems is normally impossible. So we have to rely on the observation of the output of these PS systems under normal and various pathological conditions. One of these conditions is narcolepsy. It is characterized by a profound disturbance of both the

[1] Supported by Deutsche Forschungsgemeinschaft, Project M-E 669/1.

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phasic and the tonic characteristics of REM sleep, along with a pathological interaction between REM sleep, waking and NREM sleep.

While there is quite a lot of literature on the tonic characteristics of REM sleep in narcolepsy, there are few quantitative data on the phasic components of REM sleep in this disease, except for REMs. For this reason we decided to examine more closely 3 phasic phenomena, all of which can be easily and reliably recorded in the standard polygraphic setting: the REMs, phasic activity of the mentalis muscle, recorded in the chin EMG, and the sawtooth waves in the EEG. We looked at the frequency of these phasic events and their distribution across the successive REM periods of the night. We also analysed the NREM sleep surrounding REM periods for this activity, since it has been claimed that in narcolepsy an increased amount of ambiguous sleep (i.e., sleep with characteristics of both REM and NREM) might exist (De Barros-Ferreira and Lairy 1976).

Subjects and methods

Seventeen inpatients with narcolepsy-cataplexy (10 males and 7 females), who were referred to the sleep disorders centre of the Neurological Hospital in Treysa, F.R.G., for initiation or adjustment of drug therapy, were polygraphically recorded for 3 consecutive nights, following 1 adaptation night. Antidepressant and stimulant medication was discontinued at least 2 weeks before the recording. On the recording days, the patients were instructed to avoid naps after 17.00 h. All patients included in this study suffered from sleep attacks and cataplexy, and all but one had one or more of the other auxiliary symptoms of narcolepsy (hypnagogic hallucinations, sleep paralysis and automatic behaviour).

The age and sex distribution of the sample is approximately representative of the patients with narcolepsy in this clinic. The age range was from 25 to 70 years with a median of 52 years. The onset of the disease ranged from age 5 to 37, the median was 24 years (Table I). Other major medical disorders, including depressive syndromes, were ruled out clinically. Sleep apnoea and the nocturnal myoclonus syndrome were excluded polygraphically.

The control group consisted of 17 healthy paid volunteers who were age- and sex-matched to the patients one-to-one. The maximum age difference between a patient and his control was 1 year. The recording protocol was the same for both groups. During daytime, the controls performed their usual activities; they were instructed to avoid unusual physical exertion and abstain from alcohol and drugs.

For the recording, a 16-channel Siemens Mingograph or a 17-channel Nihon-Kohden polygraph model 4217 was used; patients and controls were randomly assigned to the 2 recording units. Recording and sleep stage scoring in 30 sec epochs were done according to the standard rules (Rechtschaffen and Kales 1968).

Phasic events (REMs, twitches and STWs) were scored for all epochs of REM sleep, the epochs of NREM sleep within REM periods and for the NREM sleep during the 10 min immediately preceding and following each REM period, i.e., the 'intra', 'pre' and 'post' intervals. A REM period was considered to be finished when an epoch of REM sleep was separated from the next by 20 or more minutes of other stages (cf., Benson and Zarcone 1979). REM efficiency was calculated as the percentage of epochs of stage REM within the REM periods.

The density of phasic events was calculated by counting the number of blocks/min containing at least 1 event. The block length was 3 sec for REMs; for m. mentalis twitches and STWs, which occur less frequently, the block length was set to 10 sec.

For the evaluation of intra-night patterns of phasic activity, all nights were excluded which did not contain at least 1 REM period in each third of the night. From a total of 51 nights in each group, this criterion excluded 9 nights of narcoleptic patients and 8 nights of the controls. At least 1 night from each subject met the criterion for inclusion. Statistical analysis was limited to the first 4 REM periods of each night, because few nights had 5 or more REM periods. To compensate for the large inter-individual variance in the densities of phasic activity, relative density values were calculated

TABLE I

List of patients with symptoms at the time of the recording. Age = age at recording (years); onset = age at onset of narcolepsy (years); SA = sleep attacks; CA = cataplectic attacks; SP = sleep paralysis; HH = hypnagogic hallucinations; AB = automatic behaviour. 1 = first symptom of narcolepsy; + = symptom occurred later in the course of the disease; 0 = symptom never occurred. In one patient (HM), sleep attacks and cataplexy began at the same time.

Code	Sex	Age	Onset	SA	CA	SP	HH	AB
WR	M	25	24	1	+	0	0	+
AC	F	40	5	+	1	0	0	+
FH	M	42	24	1	+	+	+	0
CS	M	45	31	1	+	+	+	0
EW	M	49	13	1	+	+	+	0
HB	M	49	32	1	+	0	+	+
IS	F	50	24	1	+	+	+	+
BG	F	51	7	1	+	+	+	0
HF	M	52	39	1	+	0	+	+
EL	F	53	20	1	+	+	+	+
HZ	M	54	33	1	+	0	0	0
HM	M	55	37	1	1	+	0	+
GB	F	56	20	1	+	+	+	+
AG	F	57	27	+	1	0	0	+
EB	M	58	23	1	+	0	+	0
KT	M	63	26	1	+	0	+	+
EK	F	70	12	1	+	0	+	0

which express the density of a phasic event during 1 REM period in relation to the mean value of the whole night.

Definitions

For rapid eye movements, the definition from Hishikawa et al. (1978) was adopted: a rapid eye movement was scored for any deflection in the horizontal EOG tracing with an amplitude larger than 20 μV and an angle against the horizontal larger than 69° at a paper speed of 1.0 cm/sec and a gain of 7 mm/50 μV (low cut 0.3 sec, high cut 30 Hz).

An m. mentalis twitch was scored for each phasic increase in the chin EMG that was shorter than 1 sec and which reached 3 times the level of surrounding muscle tone, but at least 20 μV. Twitches found within 3 sec before or after a substantial change in muscle tone, and movement arousals, were not counted.

Any train of 3 or more consecutive EEG waves with a parallel, continuously declining, component (angle against baseline larger than 80° at a paper speed of 1.0 cm/sec, gain 7 mm/50 μV) and with a frequency from 2 to 5/sec and an amplitude between 20 and 100 μV was considered to be a sawtooth wave. Of this wave train, at least 2 waves had to display the following form: slow incline to a negative peak with a consecutive steep linear decline which ends in a positive peak. This definition is derived from descriptions and pictures of STWs in various publications (Jouvet et al. 1960; Berger et al. 1962; Schwartz 1962; Rechtschaffen and Kales 1968; Ishiguro et al. 1979). It is drawn up rather conservatively to avoid artifacts from similar wave forms of SWS. Several sleep records were scored by various experienced scorers using these definitions, and differences were mediated until a high level of agreement was reached. The scoring of the records in the study was then done by a single scorer.

Results

Tonic characteristics of REM sleep

The patients and the controls had about the same absolute and relative (per cent of sleep period time) amounts of REM sleep per night. The mean number and mean duration of the REM periods (REMPs) were not different either. In the controls, the mean duration of the successive REMPs

TABLE II

Some polygraphic sleep parameters from 17 narcoleptic patients and 17 controls, 3 nights from each individual (mean and standard deviation), P = level of significance for differences between groups.

	Narcoleptics	Controls	P
Sleep period time (min)	480 ±64	456 ±53	ns
REM sleep/night (min)	71 ±24	79 ±23	ns
No. of REM periods/ night	3.9± 0.9	4.1± 0.8	ns
Mean duration of REM period (min)	17.8±12.6	19.3±12.2	ns
REM fragments/ REM period	4.9± 3.4	4.0± 2.8	0.01

increased slightly from 18.3 min for the first to 22.6 for the fourth REMP; in the patients there was no such trend. In the patients the REMPs were more often interrupted by sequences of NREM sleep and/or stage waking (4.9 vs. 4.0 REM sleep fragments/REMP, $P < 0.01$; Table II).

Within the REMPs of the patients we found about 3 times as much stage waking as in the controls (9.5 vs. 3.6% of REMP time, $P < 0.01$). Nevertheless, REM efficiency was about the same in the two groups (79.2 vs. 77.9%), because the patients had less NREM sleep (stages 1 and 2) within the REMPs (Fig. 1).

In 29 of 51 nights of the patients a sleep onset REM period (SOREM) with a latency of less than 15 min (Montplaisir 1976) occurred. In 13 of the 17 patients at least one SOREM was registered in

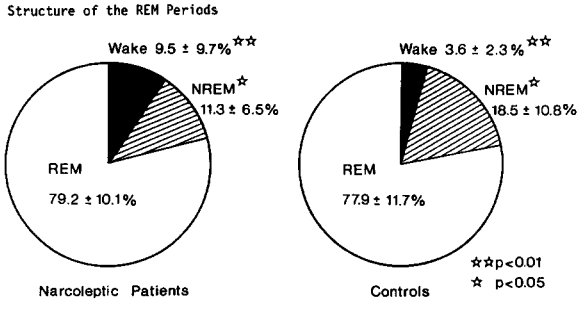

Fig. 1. Structure of the REM periods in narcoleptic patients and controls. The sectors represent the proportions of stage REM, waking and NREM sleep (combined stages 1–4) within the REM periods. Means and standard deviations are indicated.

the 3 nights. The distribution of the REM latencies showed 2 peaks, the first for latencies shorter than 5 min, the second at 60–70 min. In the controls, mean REM latency from first epoch of stage 1 was 82.0 min (median).

Phasic activity during REM sleep

The narcoleptics had about twice as many twitches of the m. mentalis/min as the controls (median 1.2 vs. 0.6 blocks/min, $P < 0.01$, U test). The inter-individual variability was considerable, with a range from 0.31 to 2.54 in the patients and 0.15 to 1.22 in the controls (Fig. 2A).

REM density, too, was higher in narcoleptics than in controls. In the patients, the median was 4.8 (range from 3.5 to 9.5) and in the controls it was 3.3 (range from 1.5 to 9.5). The difference was significant ($P < 0.05$, Fig. 2B).

For STWs, we did not find a significant difference between the 2 groups. STWs are, especially with our rather strict definition, much less frequent than REMs or m. mentalis twitches, but also show great inter-individual variability. In 2 narcoleptic patients we could find no STWs at all within the 3 nights; in 1 control we detected only a single STW train. The highest count was 96 STWs per night in a control (narcoleptics: median 0.13, range 0–0.42, controls: median 0.07, range 0.00–1.22, Fig. 2C).

The densities of REMs, twitches and STWs proved to be stable over successive nights. From the first to the third night in both groups, there was no trend towards increase or decrease for any of the 3 sorts of phasic activity. Density values were highly correlated, with r values ranging from 0.70 to 0.95 in controls and from 0.59 to 0.80 in patients. The only exception was twitch density in narcoleptics, where the correlation between first and second nights was only 0.33, while the respective value for second and third nights was 0.80.

To check for an interdependence between REM, twitch and STW densities, we calculated Spearman rank order correlations for both groups. The correlation coefficients were all between −0.24 and 0.38; none of them was significant (Fig. 3). Based on individual REMPs, there were no significant correlations between these 3 measures of phasic activity.

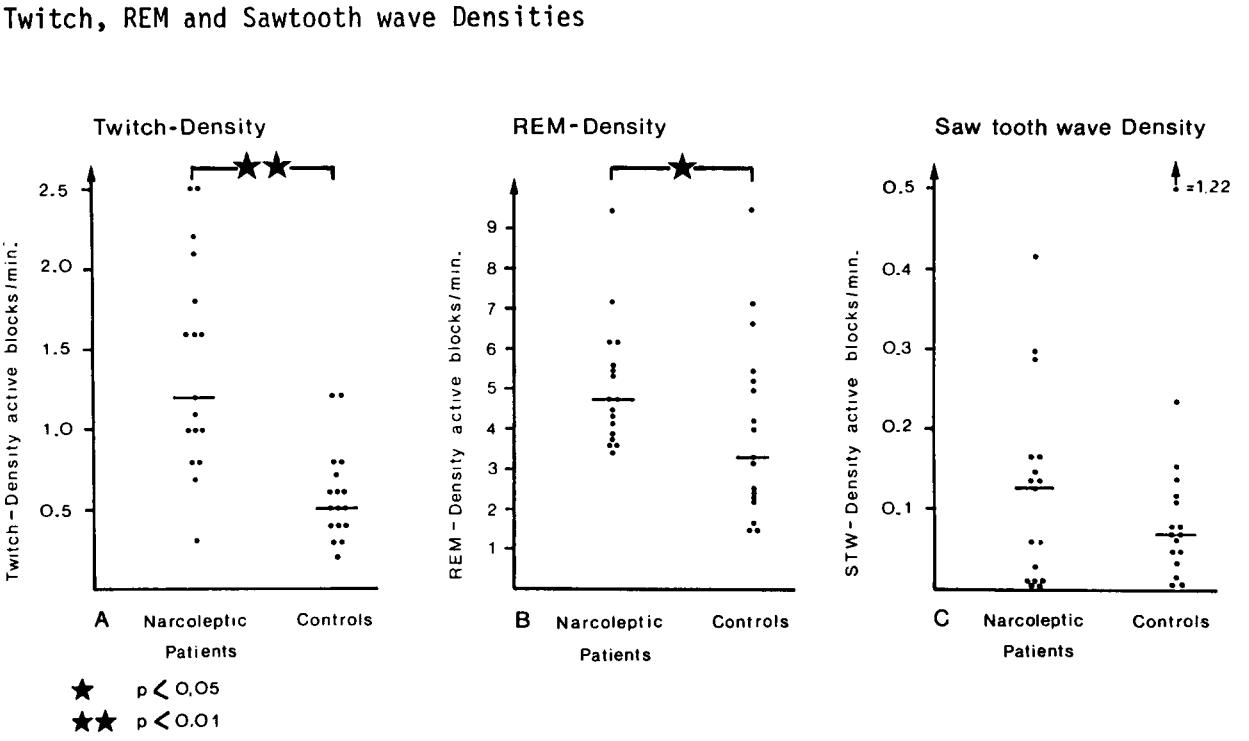

Fig. 2. Density of phasic events during REM sleep in narcoleptic patients and controls. The points represent the mean values for a single subject averaged over 3 nights, the horizontal line indicates the median. The difference between patients and controls is significant for REMs ($P < 0.05$) and for twitches ($P < 0.01$, U-test).

Other variables which could potentially influence the density of phasic activity are duration and fragmentation of the REMPs. We correlated relative REM, twitch and STW densities of each REMP with its duration and with the number of REM fragments. The Spearman correlation coefficients were all lower than 0.25 (ns), both for narcoleptics and controls.

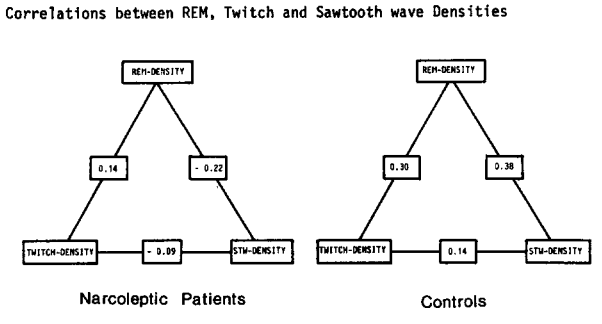

Fig. 3. Spearman rank order correlations between twitch, REM and sawtooth wave densities in narcoleptic patients and controls. The correlation coefficients are based on the mean values for 3 nights (n = 17). None of the correlations is significant.

The influence of age on phasic activity was also tested by Spearman rank order correlations. In the narcoleptics, phasic activity did not significantly correlate with age. In the controls, the rate of m. mentalis twitches decreased significantly with age ($r = -0.61$, $P < 0.01$), while REM density and STW density did not depend on age.

In the narcoleptics, we compared SOREMPs with those first REMPs which had a latency of more than 15 min. We considered only REM periods which occurred during the first third of the night. SOREMPs were slightly shorter than the "normal" first REMPs, and they were interrupted more often by NREM sleep and waking. REM density was a bit lower in SOREMPs. None of these differences was statistically significant, however. Twitch density was equal in the two cases, while the STW density was lower in the SOREMPs (Table III).

TABLE III

Comparison between sleep onset REM periods and REM periods with a latency longer than 15 min from sleep onset (first epoch of stage 1). REM periods which did not begin within the first third of the night were excluded from the analysis. Density is given as 'active blocks/min.'

	SOREMP	'Normal'	P
Number (n)	29	18	
Latency (min)	3.1 ±3.8	78.3 ±29.2	
Duration (min)	17.7 ±7.5	20.2 ±14.7	ns
REM fragments/ REM period	3.8 ±3.2	3.3 ± 2.7	ns
REM density	4.3 ±2.5	4.8 ± 1.8	ns
Twitch density	1.5 ±0.8	1.5 ± 1.1	ns
STW density	0.08±0.11	0.27± 0.46	0.05

Phasic activity during NREM sleep

Phasic activity was also scored during the 10 min before and after each REMP, and during episodes of NREM sleep within REMPs. Since we found no significant differences in the levels of phasic activity during these 3 periods, the 'pre,' 'intra' and 'post' phases were combined to yield a single 'NREM' value for statistical analysis. Note that these 'NREM' values cannot be assumed to be representative for NREM sleep in general, but only for the episodes within or surrounding REMPs, as defined above.

The density of m. mentalis twitches during 'NREM' was much lower than during REM sleep for both narcoleptics and controls. In the patients, however, NREM twitch density was about twice as high as in the controls (0.47 vs. 0.22, $P < 0.01$). During REM sleep the relation of twitch density between patients and controls was similar (1.2 vs. 0.6), and so the NREM/REM ratio of twitch density was not very much different between both groups: 0.36 in the narcoleptics and 0.39 in the controls.

STWs, which are quite infrequent during REM sleep, occur very rarely during NREM sleep. We found an STW density of 0.03 in the narcoleptics and 0.02 in controls (difference not significant); this resembles about 1 STW in 30–50 min. The NREM/REM ratio of STW density is 0.23 in the narcoleptics and 0.12 in the controls. This difference is not significant, owing mainly to the large variance in the STW density.

Within these phases, during epochs which were scored as NREM sleep stage 1 or 2, there were short sections of a few seconds duration with rapid eye movements, very low muscle tone and a low voltage mixed frequency EEG. These sections were considered to be unequivocal REM sleep, even when the epoch could not be scored stage REM, the duration of this polygraphic pattern being less than half of the 30 sec epoch. Rapid eye movements and other phasic activity during this time were not accepted as NREM sleep phasic activity.

Intra-night distribution patterns of phasic activity

In the narcoleptics mean REM density remained at an even level throughout the night. In the controls relative REM density increased significantly from the first (REMP1) to the second REM period (REMP2; paired t test, $P < 0.01$). During the following REMPs there was no further significant change (Fig. 4A and B). From REMP1 to REMP2 there was an increase in REM density in 33 of the 43 nights in the controls; in the patients, REM density increased in 22 nights and decreased in 20 nights.

Mean twitch density decreased significantly from REMP1 to REMP2 in the patients ($P < 0.01$).

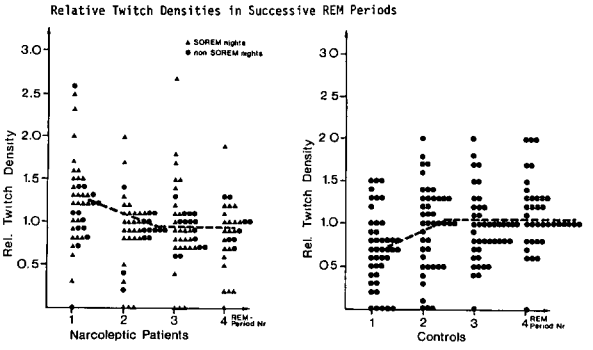

Fig. 4. Relative twitch density over successive REM periods. The dashed line gives the median values, the points represent the twitch densities of single REM periods relative to the mean twitch density of the whole night. For this analysis only nights with at least one REM period in each third of the night were selected. Additionally, 1 night from a patient had to be deleted due to technical problems with the EMG recording. In the narcoleptic patients, twitch density decreased significantly from the first to the second REM period; in the controls it increased.

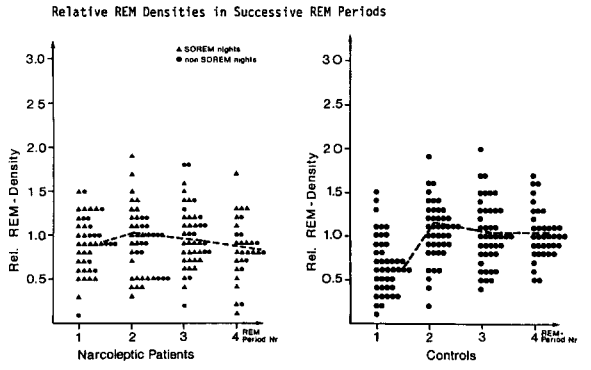

Fig. 5. Relative REM density over successive REM periods. Graphic representation and selection of nights are the same as in Fig. 4. In the controls, REM density increases significantly from the first to the second REM period; in the patients there is no significant change.

An increase was found only in 11 nights, while REM density decreased in 31 nights. The trend was the same in SOREM and non-SOREM nights; in the non-SOREM nights it did not reach the level of significance, due to the smaller number of nights in this group ($n = 14$, $5\times$ increase, $9\times$ decrease). During the rest of the night no further change occurred. The controls displayed the same pattern as for REM density: a significant increase from REMP1 to REMP2 with no further change during the rest of the night ($P < 0.01$, Fig. 5A and B). In 28 of 43 nights twitch density increased from REMP1 to REMP2.

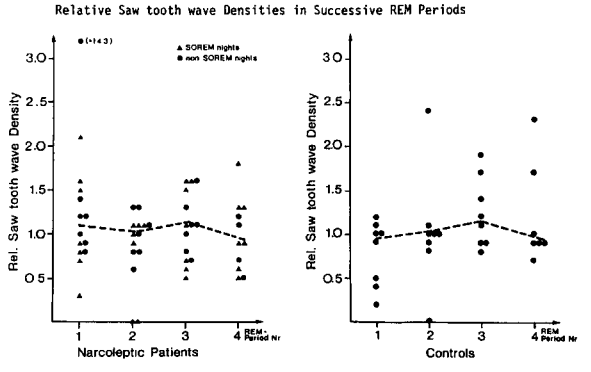

Fig. 6. Relative STW density over successive REM periods. Graphic representation and selection of nights are the same as in Fig. 4. Additionally, all nights are deleted which did not have at least 10 STWs. There is no significant change in STW density over the night.

The number of STWs was relatively low in most of the patients and controls. For the calculation of trends across the night we selected only nights with at least 10 STWs. This left only 14 nights from 9 patients and 8 nights from 4 controls for analysis. For these nights we could not establish significant differences between consecutive REM periods in either group (Fig. 6A and B).

By means of chi-square tests we checked whether changes in the density of one phasic parameter (increase or decrease from REMP1 to REMP2) were related to changes in another phasic parameter. Additionally we tested if there was a correlation between the changes in the density of phasic activity and the duration or fragmentation of REMP1 and REMP2. None of these chi-square tests showed any significant correlations in either group.

Discussion

Our results show 2 main differences between the narcoleptic patients and healthy controls concerning phasic activity:

(1) Phasic activity of REM sleep (REMs and twitches) is increased in the patients. For the STWs, we could not establish such a difference, due to the high inter-individual variability and the low overall frequency of this EEG pattern.

(2) The intra-night distribution of phasic activity is altered in the patients: while in the normals there is a considerable increase from REMP1 to REMP2 for REMs and twitches, the patients show an even distribution of REM density across the night and a decrease of twitch density from REMP1 to REMP2. Again, there are no significant differences for STWs.

For REM density, our results are in good agreement with the literature. Most authors have found that REM density is higher in polysymptomatic narcolepsy than in controls (Vejn and Jachno 1973; Meier-Ewert et al. 1975; Broughton and Mamelak 1976), though the difference was not significant in all studies (Hishikawa et al. 1978). In young healthy adults REM density rises across successive REM periods of a night (Aserinsky 1971; Benoit et al. 1974) with the strongest

increase during the first part of the night (Thomas et al. 1970; Pessah and Roffwarg 1972). In narcoleptics also an increase of REM density across the night was found by Hishikawa et al. (1978) and by Meier-Ewert et al. (1975), when averaging over 3 h periods or thirds of the night, respectively. When REM periods of equal rank number were treated separately, however, REM density remained at a plateau (Schulz et al. 1981) or decreased from REMP1 to REMP2 (Reynolds et al. 1983) in narcoleptic patients.

For m. mentalis twitches, our findings are very similar to those on REMs; the differences between patients and normals are even greater. In normals, other sorts of phasic activity have been studied, especially MEMAs (activity from the m. tensor tympani, Pessah and Roffwarg 1972) and PIPs (m. orbicularis oculi, Rechtschaffen et al. 1971). The distribution patterns of both PIPs and MEMAs are, again, similar to those of REMs and twitches. Benson and Zarcone (1979) found the lowest rates of PIPs in the beginning of the night, and Pessah and Roffwarg (1972) found an increase of MEMA density from the first to the second REM period and a subsequent slower decrease. All of these phenomena result from phasic discharge in various muscle groups; this type of activity might be considered as one 'class' of phasic activity with common properties. Other types of phasic activity which are not directly related to muscle activity, such as the STWs, could belong to other 'classes' of phasic activity. This would explain our findings on STWs which did not show the characteristic 'dip' early in the night and were not different between patients and controls.

Although there are similarities in the frequency and distribution patterns of the muscle-related phasic phenomena within the groups, these parameters appear to be relatively independent in individuals. For example, one normal subject with a 10 times higher STW density than average exhibited normal twitch and REM densities. This pattern of quantitatively independent phasic phenomena together with a similar distribution pattern suggests that the phasic activity is generated or triggered via separate pathways, but modulated by a common mechanism. For REMs and twitches these pathways have been identified at least in part: the eye movements of REM sleep are generated by the premotor neurones of the reticular formation, while the muscle twitches result from phasic excitation of the alpha motoneurones via reticular and pyramidal tract neurones (Hobson et al. 1986). For the common modulating process there are two different possible modes of action which would both be in agreement with our data: the first mode is an inhibition of phasic activity which is most powerful in the beginning of the night, the other is an increasing 'stimulation' of phasic activity in the course of sleep. In narcolepsy, a dysfunction of this system could be present, either in the form of impaired effectiveness of inhibition or of an uncontrolled permanent stimulation of phasic activity. The overall increase of phasic activity in narcolepsy, during REM sleep as well as during NREM sleep, could be explained by such a dysfunction. The dysfunction of this regulation system might also influence the tonic characteristics of REM sleep, and its increased activity throughout the day could cause some of the symptoms of narcolepsy, such as cataplexy and hypnagogic hallucinations, which are considered to be signs of dissociated REM sleep (Roth 1980).

Our data do not confirm the assumption that there is an increased intrusion of phasic REM sleep phenomena into NREM sleep in narcolepsy. The higher proportion of wakefulness within REM periods in narcoleptics suggests that in the patients the transition from REM sleep to wakefulness and back is pathologically facilitated. This is in line with the results of Schwartz and Lefebvre (1973), who found overlaps between REM sleep and wakefulness in narcoleptic patients, in the forms of 'infraclinical' awakenings and micro-awakenings. During wakefulness, incomplete micro-REM periods have been observed in some patients (Meier-Ewert 1985), and the occurrence of REM sleep directly from wakefulness during daytime is a frequent phenomenon to be seen in the multiple sleep latency test. This facilitated REM/waking transition may represent one of the basic pathophysiological mechanisms in narcolepsy.

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