Inter-REM Sleep Intervals Distribution in Healthy Young Subjects

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Neurophysiological research in animals has recently underlined the importance of distinguishing sequential from single REM episodes, suggesting a possible different functional role of these sub-species of REM sleep. In human beings it is not still clear how much time has to elapse between two sections of REM sleep before they are recognised as two separate REM episodes, and hence sequential rather than single REM episodes. To this end we analysed 76 PSG recordings from 29 healthy young subjects. On the basis of the distribution of inter-REM intervals in our sample, we empirically set a combining rule of 20 minutes to define a REM sleep cycle, and to distinguish single vs. sequential REM episodes. Out of 276 REM sleep episodes detected, 71.38% were defined as single REM and 28.62 % as sequential REM episodes. Sequential, like single, REM episodes were not prevalent in any particular sleep cycle or part of the night, even though the percentage of sequential REM episodes seems to be related to circadian REM sleep pressure. The authors point up the importance of investigating experimentally the functional significance of these two sub-species of REM sleep in humans. **(Sleep and Hypnosis 2003;5(1):1-6)**

Key words: *NREM-REM cycle, human sleep, cycle structure, REM episode, inter-REM intervals, sequential REM episodes, single REM episodes, combining rule*

INTRODUCTION

Almost fifty years have passed since the discovery of REM sleep (1). It was hoped the discovery of this kind of sleep would help explain the functional significance of sleep. The succession throughout the night of alternating periods of orthodox (NREM) and paradoxical (REM) sleep is one of the constant characteristics of sleep. Such regularity has prompted researchers to consider the NREM/REM sleep cycle as a basic cycle of sleep. Kleitman (2) suggested that such a basic cycle could be important even in wake conditions and introduced the concept of BRAC (Basic Rest-Activity Cycle).

The mean length of the NREM/REM cycle ranges between 70-110 minutes. The NREM/REM cycle ends with the end of a REM episode. However the criteria for identifying the end of a REM episode are still not clear. Indeed, while a REM (3) episode is frequently interrupted by the appearance of NREM sleep, wakefulness or movement time it is still not known how long these interruptions should last in order to establish that the REM episode is finished. In other words it is still not clear how much time has to elapse between two

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sections of REM sleep before they are assessed as two separate REM episodes. In normal laboratory conditions, REM sleep intervals have a bimodal distribution in many species such as the rat (4), cat (5), monkey (6) and human (7,8). On this basis it has been proposed to distinguish REM sleep episodes into single (uninterrupted REM sleep episodes) and sequential (REM sleep episodes fragmented by short period of wakefulness or NREM sleep) episodes[4]. However, the criteria for scoring single vs. sequential REM episodes in humans is still not standardised.

On the basis of bimodal distribution of REM sleep intervals, different cut-off intervals, varying from 30 seconds to 30 minutes, have been proposed for distinguishing REM episodes (9) (Figure 1).

distinguishing sequential from single REM episodes[4] (13,14) suggesting a possible different functional role. In rats exposure to a cold external temperature (i.e. 0° Celsius) causes a steady reduction in REM sleep, mainly associated with sequential episodes (only exposure to very cold temperatures, -10° Celsius, reduces the number of single REM episodes); the subsequent recovery of REM sleep is limited to sequential REM episodes.

The aim of this study was to identify a suitable cut-off interval to help distinguish between single and sequential REM episodes in humans by examining inter-REM intervals distribution in sleep recordings of healthy young subjects. A second aim was to investigate if sequential REM episodes are associated to a specific sleep cycle or to a part of the night.

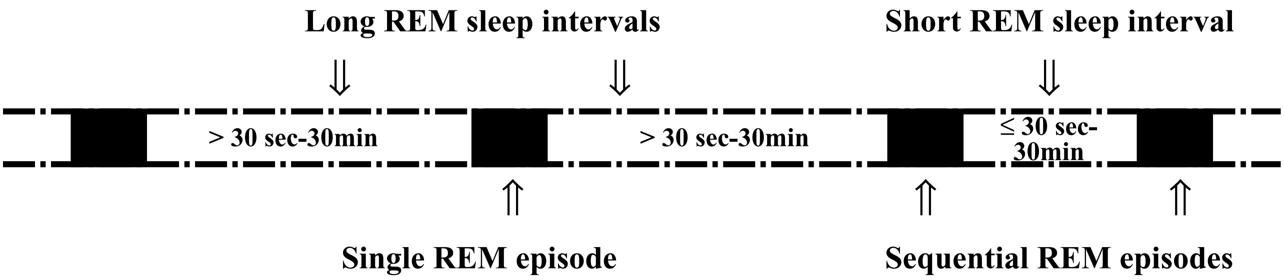

Figure 1. Schematic Representation of Sequential/Single REM episode in NREM/REM sleep cycle.
If interruption is longer than 30 sec - 30 minutes defines the NREM part of a sleep cycle, if is shorter than 30 sec - 30 minutes defines an interruption of a REM episode.

Most researchers have recommended a combining rule of 15 minutes[8] (10-12), though some have suggested setting cut-off at around 25 minutes[7]. Recently Carskadon and Rechtschaffen[3] suggested that "a combining rule of 15 to 30 min will provide the best description of REM sleep in human beings" (page 1211). In our opinion this range is too wide.

A more accurate definition of inter-REM intervals would be useful in staging and scoring procedures as well as in helping better understand the functional significance of single and sequential REM episodes in humans. Neurophysiological research in animals has recently underlined the importance of

METHODS

The present is a retrospective study based on 76 nocturnal sleep recordings obtained from 29 healthy young subjects. All subjects (15 males and 14 females, aged between 19-26, who took part in a previous research on Sleep Onset and Morning awakenings mental activity (15)) were paid university students, screened for absence of physical or psychological disorders and drug intake at the time of study. Each subject spent three non-consecutive nights (one per week) at the sleep laboratory undergoing standard electropolygraphic controls (two monopolar EEG leads, two horizontal EOG, and submental

EMG). The first adaptation night was followed by two experimental nights when subjects were awakened just once per night at time of sleep onset, stage 2 (three minutes after first sleep spindles). After this interruption subjects were allowed to sleep until they spontaneously awoke in the morning. Since in the previous experiment[15] we found no "first night effect", in the present study, besides the recordings of the two experimental nights, we also analysed adaptation night recordings.

account in our analysis.

In order to investigate a possible relationship between the presence of sequential REM episodes and REM cycle, the latter was scored. The REM cycle was scored according to the criteria of Feinberg and Floyd (17), from the onset of one REM episode to the onset of the next episode, using a combining rule of 20 minutes which was empirically set by analysing inter-REM intervals distribution in our sample (see below).

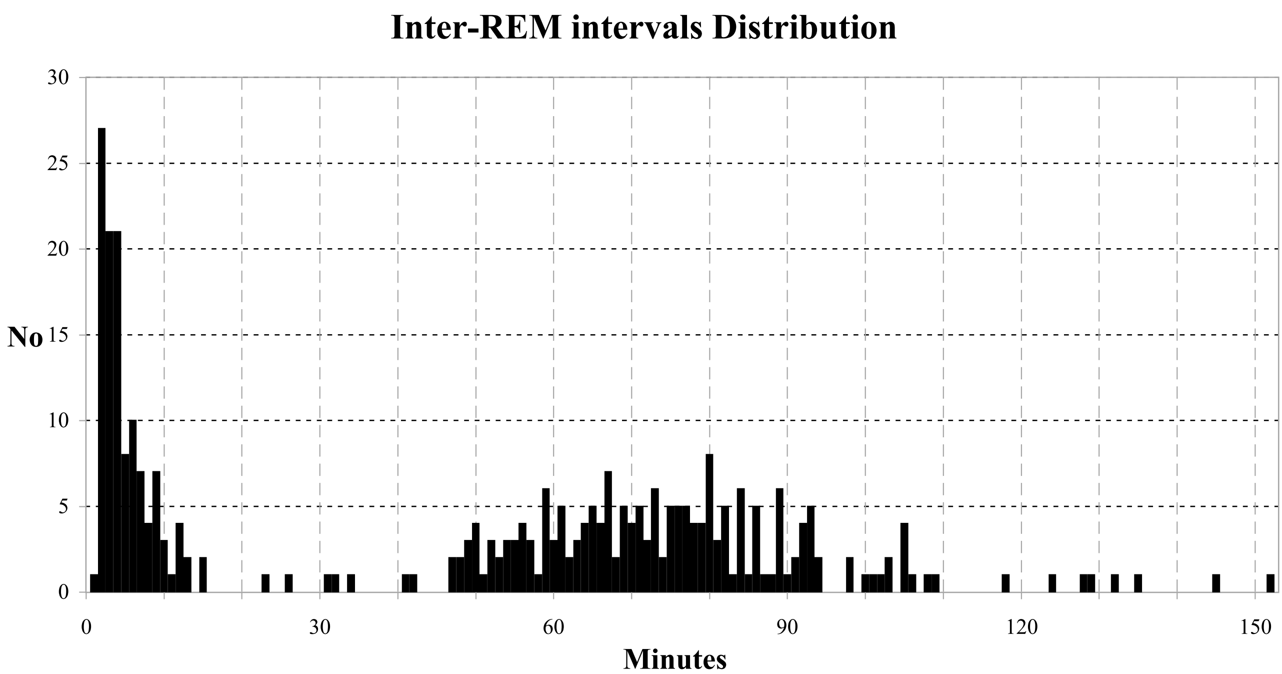

Figure 2. Distribution of inter-REM intervals measured over the entire night. The histogram represents the number of intervals per minutes.

PSG recordings were scored by two expert technicians according to Rechtschaffen and Kales criteria (16), using a scoring epoch of 30 seconds. Excluded from analysis were recordings which contained more than three consecutive minutes of wakefulness[7]. For each recording the number and the duration (in minutes) of REM episodes were calculated while the number and duration (in minutes) of inter-REM intervals were also scored. The first NREM period preceding the first REM episode cannot properly be considered a dividing point between two REMs and so was not taken into

RESULTS

As regard the all-night data, figure 2 shows that the inter-REM intervals are clearly distributed bimodally with a first distribution peaking at 2 minutes and a second distribution peaking at about 80 minutes. The trough between the two peaks is located at about 20 minutes. About 37.11% of all observed inter-REM intervals lasted less than 20 minutes (in Merica and Gaillard[8] 43% lasted less than 25 minutes). A twenty minute cut-off was also used to help distinguish single vs. sequential REM episodes.

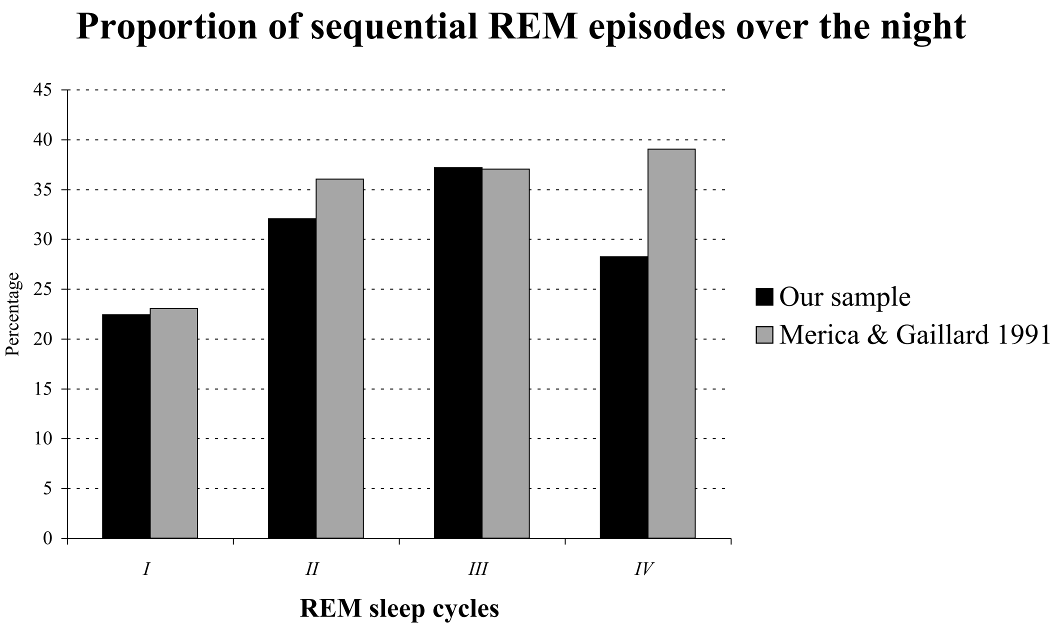

Figure 3. Distribution of Sequential REM episodes throughout the night. The histogram represents sequential REM episodes in our sample, defined using a combing rule of 20 minutes, and "sequential/interrupted" REM episodes reported in Merica and Gaillard (1991), using a combing rule of 15 minutes.

From our sample 12 subjects (41.38%) presented at least one sequential REM episode every night, 10 (34.48%) presented at least one episode in at least one night, while 7 (24.14%) presented no sequential REM episodes.

Defining a sequential REM episode as a REM stage interrupted by less than 20 minutes of NREM sleep, wakefulness or movement time, out of a sample of 276 REM episodes we found 197 single REM (71.38%) and 79 sequential REM (28.62%) episodes. The duration of REM episodes defined as sequential (20.19 min ± 11.54 min) was significantly higher than the duration of single REM episodes (17.17 min ± 11.28 min) ($F_{1,274}$=5.14, p<.05).

A twenty minute cut-off interval was also used to define REM cycles. Although a maximum of six REM cycles per night can be found in our data, not all sleep recordings present this pattern. In fact, 92.10% of the recordings presented three REM cycles, 51.32% four, 18.42% five and only 2.63% six. With this in mind we analysed data regarding the first four REM cycles only. While the presence of sequential REM episodes did not significantly change during the night (Figure 3), the duration of the episodes was significantly affected by the interaction between kind of episodes (single/sequential) and number of REM cycle ($F_{3,252}$=2.83, p<.05) (Figure 4). In particular sequential REM episodes were significantly longer than single REM episodes only in the first REM cycle (p<.05) (Tuckey test).

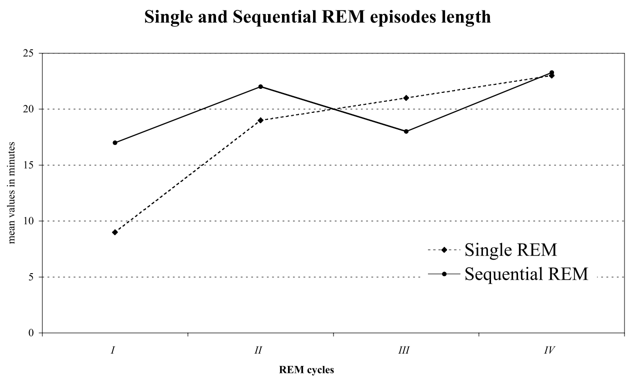

Figure 4. Single vs. Sequential REM episodes length over the REM sleep cycles.

DISCUSSION

Our results replicate those published in previous works and confirm the presence of two distinct distributions of inter-REM intervals, one (below 20 minutes) presenting an exponential distribution, the other (over 20 minutes) a normal one. A suitable cut-off between short inter-REM intervals and long inter-REM intervals seems to be 20 minutes on the basis of which a sequential REM episode can be defined as a REM episode preceded or followed by inter-REM intervals lasting less than 20 minutes, while a single REM episode is a REM episode preceded and followed by inter-REM intervals over 20 minutes (see Figure 1). In the latter case, an interruption of REM sleep of more than 20 minutes would also define the NREM/REM sleep cycle.

Besides trying establish the proper criteria for distinguishing the two types of REM episodes, another important result of this study was to describe the phenomenon of single and sequential REM episodes. In our sample 28.62% of REM episodes were sequential, a type of REM sleep that lasts longer than typical single REM episodes, particularly in the first sleep cycle. In our sample neither the number of sequential REM episodes nor the number of inter-REM short intervals seemed to be significantly related to any specific sleep cycle or to a part of the night, even if it is interesting to note how the trend of sequential REM episodes throughout the night was very similar to REM sleep pressure patterns and the opposite of body temperature rhythms (18). In our sample the percentage of sequential REM episodes was lower at the beginning of the night (when there is a marked prevalence of slow wave sleep versus REM and body temperature is falling), and at the end of the night (when need of REM sleep has already been satisfied and body temperature is already rising).

In view of the loss of homeostatic physiological equilibrium that characterises REM sleep in mammals (e.g. variability in heart rate and arterial blood pressure, irregular respiratory rhythm, etc) (19), it may be that sequential REM sleep helps prolong the duration of REM sleep with less risk for homeostatic regulation. As suggested by Amici and co-authors 13 the partition of REM sleep into single and sequential episodes could reflect two homeostatic processes: one related to the regulation of physiological variables, the other related to the regulation of the amount of REM sleep.

Is sequential REM in humans merely a phylogenetic left-over or does it have an important functional role? None of the works mentioned above, ours included, have directly assessed sequential REM, thus limiting any conclusion. Moreover the few results published are somewhat discordant. For example if our data are in line with those of Merica and Galliard[8] as regards interval distribution they differ as regards the number of sequential REM episodes that tendentially occur during the night. Given that very different functional roles may underpin these two types of sleep we feel it is important that further ad hoc experiments be carried out in man.

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