Relationships between the number of ultradian cycles and key sleep variables in outpatients with major depressive disorder

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Abstract

The regulation of the alternation between rapid eye movement sleep (REMS) and non-rapid eye movement sleep (NREMS) is still a matter of much debate. It is also an important topic for psychiatric research, since both sleep components show anomalies in Major Depressive Disorders (MDD) and related syndromes. In previous studies on healthy controls, we showed preferential links of the number of ultradian cycles with REMS-related variables rather than with NREMS-related variables. REMS Latency (RL), for example, was shown to be inversely related to the number of cycles. The present study replicates these analyses in a group of 29 patients with MDD (age range: 23–56; 16 females), after two adaptation nights. Results showed significant correlations between the number of cycles and REMS, and between the number of cycles and RL, whereas correlations with NREMS were not significant. This indirectly supports regulation hypotheses considering REMS as the main focus of the oscillation, inhibiting and interrupting NREMS. Also, when the RL is shorter, there are more ultradian cycles than when the RL is long. This adds an interesting element in the elucidation of the physiological meaning of anomalies of RL.
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1. Introduction

Sleep of most homeothermic species shows the alternation of two easily distinguishable physiological states: rapid eye movement sleep (REMS) and non-rapid eye movement sleep (NREMS). Healthy humans have two to seven NREMS–REMS "cycles" in a night, rodents may show up to 125 alternations in 24 h, in what appears to be a genetically mediated pattern linked to brain weight (Zepelin, 2000). The respective functions of these two sleep components, the nature of their interrelationships, the reason why they alternate and the regulation of this cycling are a matter of much debate and have generated several hypotheses.

It is generally accepted nowadays that ultradian cycling is "sleep-dependent" rather than result of a clock independent of sleep, as the notion of a basic rest–activity cycle has not found enough experimental support (Kleitman, 1963). Schematically, the remaining hypotheses on the regulation of the alternation can be classified into two main groups.

1. One sleep state is cycling; the other fits in: Here, REMS and NREMS compete for expression. Pressure

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for both sleep states would be accumulated mostly during wake (or absence of sleep). Two alternatives are possible here.

1a. NREMS cycles: the *primum movens* of the ultradian cycling process is NREMS. This is especially attractive in view of the distribution of delta EEG activity in NREMS, i.e. slow-wave activity (SWA), in human sleep spectrograms, where successive waxing and waning of low frequency waves seem to be permissive of REMS once a threshold is crossed in the descending slope. Here, SWA episodes may appear to reflect some (yet undiscovered) neuroendocrinal pulses (Feinberg, 1974; Feinberg and March, 1988). An ancillary role for REMS would notably explain the fact that this sleep state, although ubiquitous early in life, can be suppressed for quite long periods without evident negative consequences in human adults, in what has been proposed to be a "default state" (Horne, 2000).

1b. REMS cycles: the *primum movens* of the ultradian cycling process is here REMS, inhibiting and interrupting NREMS in function of its own regulation. This is compatible with the concept of short-term (less than 24 h) homeostasis (Vivaldi et al., 1994). Manipulations of rat sleep during the early part of the night and observations of the recovery during the latter part support the idea that short-term REMS homeostasis is largely independent of intercurrent NREMS (Ocampo-Garcès et al., 2000; Ocampo-Garces and Vivaldi, 2002; Vivaldi et al., 2005).

2. REMS–NREMS cycles: here REMS and NREMS episodes are closely linked together, and form "miniature sleep units" (Kobayashi et al., 1985).

2a. Clock-like REMS–NREMS cycles: here REMS and NREMS episodes are considered as alternating following a reciprocal interaction at the command level (Limit-Cycle Reciprocal Interaction Model; McCarley and Hobson, 1975; McCarley and Massaquoi, 1986; Massaquoi and McCarley, 1992). This model was developed after the discovery that opposing groups of cells in the brainstem ("REM-on" and "REM-off") are active in parallel with the presence of REMS and with the absence of REMS (Hobson et al., 1975).

2b. homeostatic REMS–NREMS cycles: here REMS propensity is seen as accumulating only during NREMS (Benington and Heller, 1994a,b), or partly during NREMS for the short-term homeostasis and during waking and NREMS for the long-term (over more than 24 h) homeostasis (Franken, 2002). REMS is seen here as a complement to NREMS, necessary for its expression

or rejuvenation. Some (yet uncovered) metabolic interchange is postulated. There would be no "memory" from one REMS–NREMS cycle to the next.

As long as the physiological evidence for this regulation is incomplete, we can only speculate on the basis of indirect arguments. One of the ways to clarify this issue is to examine the relationships of cardinal characteristics of the cycling, as the number of ultradian cycles, with NREMS or Slow Wave Sleep (SWS), REMS and the REMS Latency (RL). If REMS and NREMS compete against each other (Hypotheses 1a and 1b), the relative pressure for their expression may be translated into duration of episodes and/or number of cycles. It seems reasonable to predict both a higher number of cycles and longer duration of episodes in cases of higher pressure for a sleep state, and thus a positive link between these two variables. In any case, it seems more consistent for any sleep regulation mechanism to present a link between the number of cycles and the duration of the concerned sleep state than with the other. The links between the number of cycles and the other sleep state would be either not significant or inversely correlated (as there may be competition for a given total sleep duration). Thus pacing associated with NREMS (1a) would predict a positive correlation between the number of cycles (NCy) and NREMS; pacing associated with REMS (1b) would predict preferential links between the NCy and REMS. In the case of miniature sleep units (2a and 2b), no particular relationships should be expected between the NCy and REMS or NREMS, since the duration of one state is mostly related to the duration of the other within the dyad.

In a preceding study on healthy humans recorded at home, we showed preferential relationships of NCy with REMS, thus supporting the hypothesis of REMS-based oscillators (Le Bon et al., 2002a). The total SWA per night was shown not to differ whether the night included a few or many cycles (Preud'homme et al., 2000; Le Bon et al., 2005), whereas the SWA per cycle was inversely related to the number of cycles, at least in Cycle 1 (Le Bon et al., 2005). Preferential links of the NCy with REMS were also found in mice (Le Bon et al., 2007).

These relationships matter in psychiatric research, where major depression has been repeatedly associated with anomalies in both REMS (shorter RL, flatter REMS distribution, increased REMS density) and NREMS (reduced SWA and NREMS). In an earlier article, we demonstrated inverse links between NCy and RL in healthy controls (Le Bon et al., 2001a), thus suggesting that major depression might be associated with more