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# Sleep ultradian cycling: Statistical distribution and links with other sleep variables, depression, insomnia and sleepiness—A retrospective study on 2, 312 polysomnograms

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ABSTRACT

The number of alternations between Non-Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep in humans is usually considered to consist of 4–5 cycles of about 90 minutes duration per night. Previous studies by our group showed a normal distribution on 26 healthy human subjects. The present study retrospectively analyzes the polysomnograms of 2,312 unmedicated patients who were admitted for medical and/or psychiatric reasons in the Erasme University Hospital between 2003 and 2014. The normal distribution of the Number of Cycles and Mean Cycle Duration was confirmed. Q-Q plots were very close to linearity. This distribution allows the use of these variables in parametric comparisons. The Number of Cycles per night and the Mean Cycle Duration showed predominant links with REM sleep-related variables, such as the REM Latency, REM sleep duration, the REM/NREM sleep ratio. None of these variables was associated with the diagnosis of Major Depressive Disorder, nor the intensity of Depression as measured by the Beck Depression Inventory (short version). On the other hand, the diagnosis of Major Depressive Disorder was significantly associated with the Insomnia Severity Index and correlated with the intensity of depressive symptoms (Beck Depression Inventory).

## Introduction

Polysomnograms of human sleep show two distinct physiological states: Rapid Eye Movement (REM) sleep and Non-Rapid Eye Movement (NREM) sleep. Healthy adult sleep begins with NREM, switches to REM after some time, then switches back and forth a certain number of times from one state to the other. The night may end either in REM or in NREM. This alternation along the night follows rules that are still poorly understood (see for instance Le Bon and Linkowski, 2013).

Sleep cycles are defined as NREM episodes immediately followed by a REM episode. The number of REM sleep episodes is thus equal to the number of cycles. The number of NREM episodes is equal to the number of cycles, superior by one if the night ends in NREM or inferior by one if the sleep starts by REM sleep as in narcolepsy. These cycles are called ultradian as they are shorter than the day.

A few studies performed between 1968 and 1985 have described the number of sleep cycles per night (NCy) varying from 2 to 7 (Brezinová, 1974; Clausen et al., 1974; Hartmann, 1968; Kripke, 1972; Sterman and Hoppenbrouwers, 1971; Merica and Gaillard, 1985). However, the NCy in a healthy human adult is still usually considered in sleep research today to be equal to 4 or 5. It is generally seen as a solely descriptive characteristic of sleep, not influencing the content of sleep cycles, such as the duration or the intensity of NREM, the duration of REM or the ratio between them. For instance, studies have been performed comparing the first to the second cycle in the same night, or the first cycle between clinical groups (Ganguli et al., 1987; Gillberg and Akerstedt, 1991; Lauer et al., 1995; Reynolds, 1987; Rotenberg et al., 2002). The mean cycle duration (MCD) for its part is generally considered to last about 90 minutes. Indeed, 4–5 cycles of 90 minutes correspond to an average night of 360–450 minutes. This view has been challenged in previous studies by our research group on 26 healthy subjects studied at home. The NCy was shown to spread from 2 to 7 and the MCD was shown to spread from 22 to 225 minutes. These variables were shown to follow a normal (Gaussian) distribution and to have the potential to be used in parametrical comparisons (Le Bon et al., 2005, 2002, 2001). An inverse association between the NCy and the REM sleep latency (REM-L), first observed by Merica and Gaillard (1985) was confirmed in this group (Le Bon et al., 2001). We have also shown that the spectral

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power of the first cycle is inversely dependent on the number of REM episodes during that night (Le Bon et al., 2005). A Gaussian distribution of NREM-REM cycles has also been shown in mice (Le Bon et al., 2007) and rats (Le Bon et al., 2009), where the number of alternations is about twenty times more frequent than in humans.

The present study had for aims: 1) to confirm the normal distribution of the NCy and the MCD in a much larger group of humans; 2) if the normal distribution was confirmed, to analyze links between the NCy and MCD, and other sleep variables, including the REM-L; 3) to analyze links between the NCy and MCD, Major Depression, Depressive symptoms intensity, insomnia and sleepiness.

## Methods

### *Subjects*

All recordings from patients having performed a polysomnogram in the sleep unit of the Erasme University Hospital between January 2003 and December 2014 were considered ($n = 3{,}511$). Since only a minority of these patients was subjected to a second consecutive night of recording, only first nights were examined in the present study.

These individuals had presented themselves to the sleep medicine consultation, either spontaneously or through their referring physician (general practitioner/non-psychiatric specialist/psychiatric specialist). During this visit, a physician specializing in sleep medicine performed a preliminary assessment of complaints related to sleep, ongoing treatments, somatic and psychiatric comorbidities, in order to propose a first diagnostic hypothesis. Following this assessment, a sleep laboratory polysomnogram was offered, in order to exclude the presence of sleep pathology and obtain an objective sleep evaluation. Moreover, the data collected during the ambulatory consultation were systematically confirmed when the subjects were admitted to the sleep laboratory.

Upon admission to the sleep laboratory:

- These individuals had their medical records reviewed and a complete somatic check-up performed, including a blood test (liver and kidney function tests, hematology profile, thyroid function tests), electrocardiogram, a daytime electroencephalogram, urinalysis, and a chest X-ray (only for those over the age of 45 years). These steps allowed for a systematic diagnosis of potential somatic pathologies present in people admitted to our unit.
- They benefited from an appointment with a unit psychiatrist who potentially assigned psychiatric diagnoses using the DSM IV-TR criteria (American Psychiatric Association, 2000).
- A psychiatrist of the unit conducted a sleep-specific medical record systematic review to complete an assessment of complaints related to sleep including sleeping habits, severity of self-reported insomnia complaints (difficulty falling asleep, repeated nighttime awakenings, early morning awakening, and non-restorative sleep), symptoms of sleep apnea (snoring and self-reported apneas), symptoms of restless legs syndrome (drive to move the legs often, accompanied by abnormal leg sensations—symptom worsening at rest, that is, sitting—partial or temporary relief by activity, at least as long as the activity continues—worsening of the symptoms later in the day or night), and nocturnal movements (e.g., periodic limb movements (PLM) during sleep).
- They completed a series of self-questionnaires to assess the severity of their subjective complaints of depression, poor sleep, and EDS as follows: insomnia severity measured by the Insomnia Severity Index (ISI, Morin et al., 2011), excessive daytime sleepiness measured by the Epsworth sleepiness scale (ESS, Johns, 1991)) and intensity of depressive symptoms measured by the Beck Depression Inventory, Short version (BDI-SF, Beck et al., 1974, 1961).

These different assessments made it possible not to include in our research database the individuals with the following pathologies: uncontrolled heavy psychiatric disorder (such as psychotic disorders), presence of uncontrolled heavy somatic disease (chronic liver disease, chronic pancreatic disease, chronic pulmonary disease, severe cardiovascular disease, severe renal disease, autoimmune disease, and pathologies altering the activity of hypothalamic-pituitary-adrenal axis as Cushing's syndrome), presence of inflammatory or infectious disease, presence or history of cranial trauma, presence or history of central nervous system injury that could involve respiratory centers in the brain, presence or history of craniofacial or thoracic cavity malformations, presence of pregnancy, presence of Obstructive Sleep Apnea Syndrome (OSAS) already known or course of treatment before sleep laboratory, presence of PLM disorder/RLS already known or course of treatment before sleep examinations, presence of predominantly central apnea syndrome, presence of narcolepsy or primary hypersomnia, presence of parasomnia, presence of circadian sleep disorders, presence of shift work or recent transmeridian flights and presence or history of substance abuse.

Patients who took any antipsychotic, antidepressant, benzodiazepine receptor agonists or mood stabilizer within the last two weeks before their sleep recording were excluded from the present analysis ($n = 1{,}120$). None of the individuals included in our research database used over-the-counter sleep aids (such as melatonin or herbal medicines) since these individuals were instructed to stop them at least two weeks before the sleep laboratory. Patients with a Total Sleep Time less than four hours were excluded ($n = 79$) in order to avoid the most atypical nights. The final group thus included 2,312 subjects.

### *Sleep recording*

Patients went to bed and got up at their usual times. During bedtime hours, the subjects were recumbent and the lights were turned off. They awoke spontaneously in the morning, and daytime naps were strictly prohibited. Patients had a minimum of six consecutive hours of recorded time in bed.

Polysomnograms were recorded with a 19-channel digital polygraph (Brainnet™ MEDATEC, Brussels, Belgium). Two electrooculograms (EOG), three electroencephalograms (Fz-Ax, Cz-Ax, Oz-Ax, where Ax is the left mastoid reference), one submental electromyogram (EMG), and electrocardiographic activity (ECG) were recorded. EEG montage (Fz-Ax, Cz-Ax, and Oz-Ax) is a variant of EEG montage recommended by AASM (F4-A1, C4-A1, and O2-A1) that is used specifically in our sleep laboratory for clinical and scientific activity (Hein et al., 2019a, b; Lanquart et al., 2018). Oxyhemoglobin saturation was measured using pulse-oximetry (Masimo MS-7, Irvine CA), oro-nasal airflow was detected with thermistors (Infinity™, Sleepmate Technologies, Midlothian, VA), thoracic and abdominal respiratory movements were recorded with piezoelectric sensors (Resp-EZ™, Sleepmate Technologies, Midlothian, VA), and leg movements were detected with ankle piezoelectric movement strain gauges (Moving Images, Sleepmate Technologies, Midlothian, VA). Each 20 s epoch was visually scored according to standard criterion (Rechtschaffen and Kales, 1968). The definition of N3 followed the American Academy of Sleep Medicine guidelines (Iber et al., 2007).

The polysomnographic data collected were as follows: time in bed (TIB) was the lapse between lights-out and wake-up time, sleep latency (time from lights out until the appearance of the first epoch of stage I, II, III, IV or REM), sleep efficiency index (SEI) ([*total sleep time/time in bed*]*100), sleep period time (SPT) (time in bed - [sleep latency + time awake before standing up]), total sleep time (TST) (sleep period time—awake time during night), REM latency (latency between the first epoch of stage 2 and the first epoch of REM without excluding wake time after sleep onset) as well as the percentages of stage 1, stage 2, stage 3, REM sleep, and wake after sleep onset during sleep period time. Sleep Onset REM Period (SOREMP) were considered positive when the REM-L was $\leq$ 15 minutes. Short REM-L was considered for those subjects with a REM-L $>$ 15 and $\leq$ 60 minutes. Average REM-L was considered for those subjects with a REM-L > 60 and ≤ 120 minutes. Long REM-L was considered for those subjects with > 120 minutes REM-L. Sleep onset was defined as the appearance of the first epoch of stage I, II, III, IV or REM.

The first NREM episode began with the first epoch of stage 2 or 3, and ended with the first REM episode. Each REM episode began with the first epoch of REM and ended when the last epoch of REM was followed by at least 15 min of NREM sleep or the end of the night (Feinberg and Floyd, 1979; Merica and Gaillard, 1991). The NCy was defined as each REM episode and the NREM period immediately preceding it, going back to sleep onset (1st NREM-REM cycle) or to the limit of another REM episode (from the second NREM-REM cycle to the end of the night). New variables were created to disentangle the issue of night duration (see later): the NCy/TST(min) was the number of cycles (*100) divided by the TST; NCy/SPT(min) and NCy/TIB(min) were respectively the same for SPT and TIB. MCD was SPT/NCy.

Apneas were scored if the decrease in airflow was ≥ 90% for at least 10 seconds and hypopneas were scored if the decrease in airflow was ≥ 30% for at least 10 seconds with a decrease in oxygen saturation of 3% or followed by a micro-arousal (Berry et al., 2012). Apnea-hypopnea index (AHI) corresponds to the total number of apneas and hypopneas divided by period of sleep in hours. Moderate to severe OSAS was present when AHI was ≥ 15/hour (Fleetham et al., 2006).

The study was conducted in accordance with the rules and regulations for clinical trials stated by the World Medical Assembly in Helsinki.

### *Biostatistical analyses*

The statistical procedures were performed using IBM SPSS version 23. Skewness was used to measure the asymmetry of the sample, and kurtosis was used to estimate the curvature (flatness/peakedness) deviations from normality. Ideally, skewness and kurtosis should be as close as possible to 0 for a sample to be considered normally distributed. Skewness values from −0.5 to 0.5 are usually considered very close to normality. Kurtosis values from −3 to 3 are often considered as acceptable, although there is no universal consensus. A Log10 transformation was applied to the MCD for a complementary estimate of its kurtosis. Q-Q plots graphically compared the expected and the observed distributions. Cohen's *d* test were used for effect size estimation, Pearson's *r* for correlations, MANOVA and Student's *t*-tests for group comparisons. All analyses were performed with a type I error set at 0.05.

## Results

A total of 2,312 polysomnograms were examined, and all medical/psychiatric diagnoses were pooled as one group. The male/female ratio was 2.11. Age range was 18–83 years (mean: 45.5; SD: 12.9). BMI range was from 15.7 to 68.2 (mean: 27.9; SD: 5.9). Caffeine use was above 100 g in 74.2%; Tobacco use was above 5 cigarettes/day in 21.5%; Alcohol use was over 30 g/day in 22.8%. Present or past episodes of Major Depressive Disorder were positive in 20.5%. Missing values for the REM-L: $n$ = 11; ISI: $n$ = 183; ESS: $n$ = 88.

The distribution of the NCy and MCD in a night is shown in Table 1. The value that appeared the most frequently (distribution mode) was at 4 cycles/night in the whole group. The combined percentage of nights with 4 or 5 cycles was 35.4% + 26.1% = 61.5%. 26.7% had fewer cycles and 11.8% showed more cycles. The mode for MCD were between 100 and < 120 min ($n$ = 745, 32,2%), while 815 subjects (35.1%) had MCD shorter than 100 min and 752 (32.5%) had MCD equal or longer than 120 min.

Table 2 shows descriptive statistics and normality testing for sleep cycles, duration and relevant sleep parameters and ratios. The skewness of the NCy sample was 0.22 and the kurtosis was 0.34. The skewness of the MCD sample was 3.5 and kurtosis was 22.4. A Log10 transformation was applied and kurtosis on the transformed MCD was estimated at 3.1. Both variables thus indicate a normal distribution (see below).

**Table 1**
NCy and MCD frequencies.

| NCy Cycles | *n* | % | MCD (SPT) Min | *n* | % |
|---|---|---|---|---|---|
| | 2,312 | 100 | | 2,312 | 100 |
| 1 | 15 | 0.6 | < 60 | 4 | 0.2 |
| 2 | 117 | 5.1 | 60– ≤ 80 | 166 | 7.2 |
| 3 | 485 | 21.0 | 80– ≤ 100 | 645 | 27.9 |
| 4 | 818 | 35.4 | 100– ≤ 120 | 745 | 32.2 |
| 5 | 604 | 26.1 | 120– ≤ 140 | 319 | 13.8 |
| 6 | 211 | 9.1 | 140– ≤ 160 | 245 | 10.6 |
| 7 | 51 | 2.2 | 160– ≤ 180 | 78 | 3.4 |
| 8 | 9 | 0.4 | 180– ≤ 200 | 22 | 1.0 |
| 9 | 2 | 0.1 | > 200 | 88 | 3.8 |

Legend: NCy, Number of Cycles; MCD, Mean Cycle Duration, measured over Sleep Period Time. The values that appeared the most frequently (distribution modes) were NCy 4, and MCD between 100 and 120 minutes.

**Table 2**
Descriptive statistics and normality testing.

| | *n* | Mean | SD | Skewness | Kurtosis |
|---|---|---|---|---|---|
| NCy | 2.312 | 4.20 | 1.16 | 0.22 | 0.34 |
| MCD | 2.312 | 116.9 | 39.7 | 3.5 | 22.4[£] |
| TIB | 2.312 | 495.30 | 52.23 | 0.24 | 3.18 |
| SPT | 2.312 | 455.51 | 56.89 | 0.11 | 1.82 |
| TST | 2.312 | 393.27 | 61.89 | −0.08 | −0.29 |
| NCy/TIB | 2.312 | 0.84 | .21 | 0.02 | 0.21 |
| NCy/SPT | 2.312 | 0.92 | 0.22 | 0.02 | 0.31 |
| NCy/TST | 2.312 | 1.07 | 0.26 | 0.71 | 3.18 |

Legend: NCy, Number of sleep cycles per night; MCD, Mean cycle duration; TST, Total sleep time; SPT: Sleep period time; TIB: Time in bed; NCy/TST, SPT, TIB: Number of cycles *100 by TST, SPT, TIB. Skewness could be considered negligible for NCy, TIB, SPT, TST, NCy/TIB and NCy/SPT. It was slightly excessive for NCy/TST and poor on MCD. Kurtosis was negligible for NCy, SPT, TST, NCy/TIB and NCy/SPT. It was slightly excessive for TIB and NCy/TST. It was poor for MCD. £ : Kurtosis of Log10 MCD was 3.1.

As longer nights could be associated with more cycles than shorter ones, night duration variables must logically be taken into account. As the night durations were naturalistic and not limited, their distribution was also tested. The three sleep duration variables (TIB, SPT, TST) were shown to have relatively small levels of skewness and acceptable levels of kurtosis.

Fig. 1 presents a 6-panels picture of histograms and Q-Q plots for NCy, SPT and NCy/SPT. Similar results were obtained for NCy/TST and NCy/TIB and are not shown as supplementary material.

The NCy distribution could be influenced, among others, by variables or factors such as Gender, Age, BMI, AHI, PLM index (PLMI), Beck Depression Inventory scores, Present or Past Major Depressive Episodes, use or abuse of caffeine, alcohol or tobacco. The patient database was broken down by these categories (top panel). In the bottom panel, four subgroups of REM-L were also presented for descriptive reasons (Table 3).

Males had slightly more cycles than females. Younger subjects had more cycles than older ones. Subjects with a higher BMI had fewer cycles. Subjects with higher AHI had fewer cycles. A higher PLMI was associated with a smaller NCy. No difference between BDI scores or present or past MDD diagnosis was observed. The NCy was not associated with presence or not of caffeine or alcohol use but was linked to tobacco consumption. A large difference was observed between patients with shorter and longer REM-L. Effect sizes were small for Gender, Age, BMI, AHI and use of caffeine; they were large for PLMI. Every

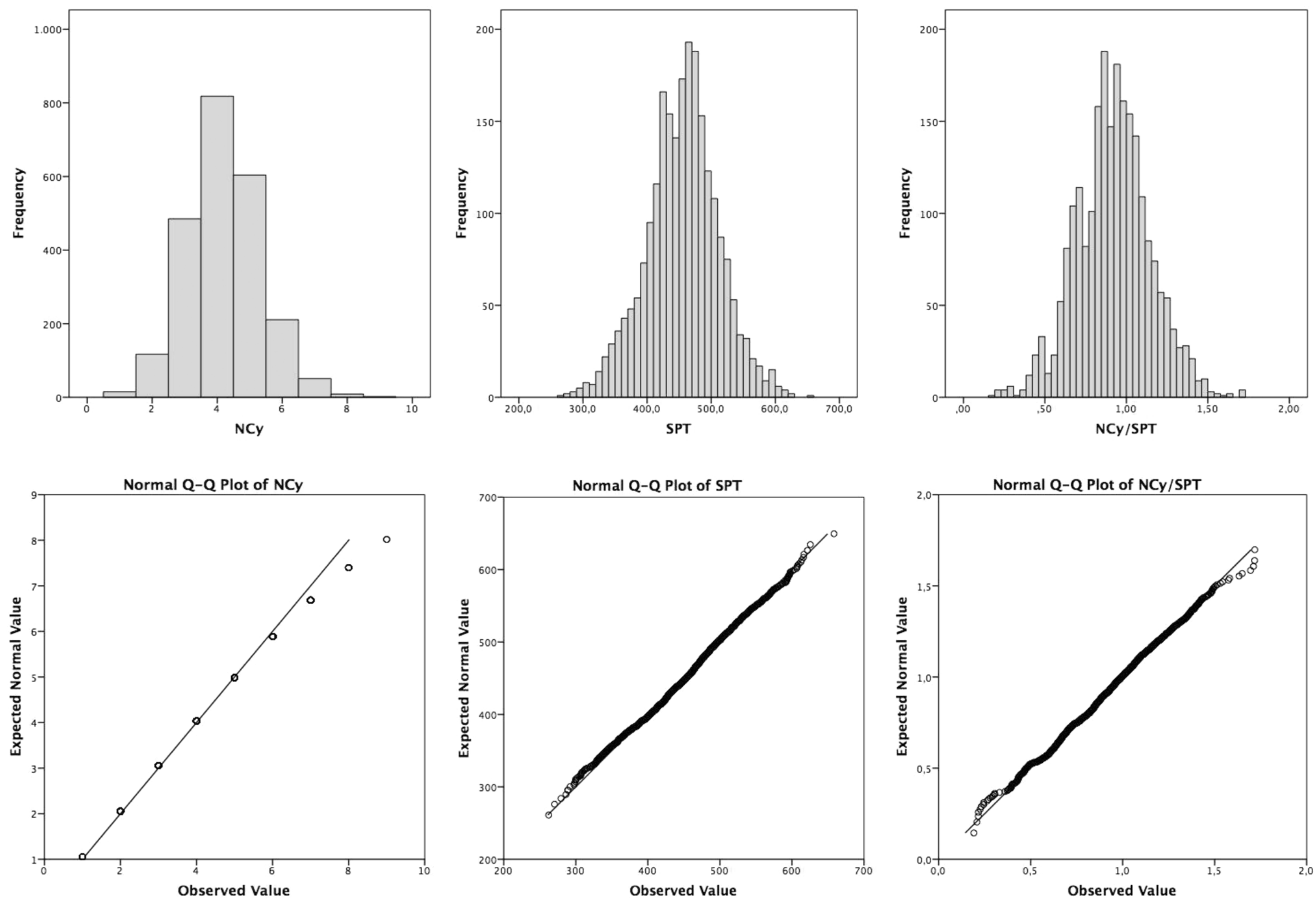


**Fig. 1.** Histograms and Q-Q plots of the Number of Cycles, SPT and NCy/SPT. Legend: *Superior row, histograms*: The Number of Cycles (NCy) distribution was very close to the normal Gaussian curve; the Sleep Period Time (SPT) curve was slightly leptokurtic (peaked); NCy/SPT was acceptably normal. *Inferior row, Q-Q plots* : A very close association was observed for the NCy curve.

subcategory showed a normal NCy distribution.

The NCy and MCD were then used in comparisons with some relevant sleep and clinical variables (Table 4). To evaluate the influence of sleep duration variables, comparisons also included NCy/SPT.

By decreasing order of association strength, the most substantial links with the NCy were:

NCy/SPT ($r = 0.888$); MCD ($r = -0.773$); Total Sleep Time ($r = 0.518$); REM-L ($r = -0.484$); Sleep Period Time ($r = 0.472$); REM duration ($r = 0.452$) NREM duration ($r = 0.405$), TIB ($r = 0.380$); REM/NREM ratio ($r = 0.265$).

Comparing respective correlations with NCy/SPT and NCy, the links with N3 were weak in both cases ($r = 0.035$ vs $r = 0.081$). Links of NCy/SPT with NREM were much weaker compared to NCy with NREM ($r = 0.102$ vs $r = .405$). Links of NCy/SPT with REM were weaker compared to NCy with REM ($r = 0.298$ vs $r = 0.452$). They remained similar for the REM/NREM ratio ($r = 0.253$ vs $r = 0.265$). Links with the REM-L were stronger using NCy/SPT than NCy ($r = -0.581$ vs $r = -0.484$).

Among other relevant links in the table, we note that Age was positively linked with the AHI index ($r = 0.260$) and inversely linked with N3 ($r = -0.478$), TST ($r = -0.314$), NREM ($r = -0.263$), REM ($r = -0.243$). The AHI was positively correlated with BMI ($r = 0.346$) and PLMI ($r = 0.223$), and inversely with REM ($r = -0.243$). REM was positively linked to the REM/NREM ratio ($r = 0.880$) and inversely linked to the REM-L ($r = -0.322$). The REM/NREM ratio was inversely linked with NREM ($r = -0.188$). The REM-L was inversely linked to NCy ($r = -0.484$), NCy/SPT ($r = -0.581$) and the REM/NREM ratio ($r = -0.357$). BDI was linked to the ISI ($r = 0.447$). The ESS was also linked to the ISI ($r = 0.218$).

Past or present Major Depressive Episode was introduced as a factor in a MANOVA analysis. Pillai's Trace: $F = 17.92 - p < 0.001$. The univariate comparisons are shown at Table 5. Cohen's *d* were medium for the ISI and large for BDI.

The odd ratio for Present or Past diagnosis of Major Depression and Female gender was 2.44 (Fisher's exact test $p < .001$). Odd ratios for SOREMP, Short REM-L and Long REM-L were not significant.

## Discussion

The first objective of the present retrospective study was to confirm the normal distribution of the NCy and the MCD.

For the first time, the distribution of the NCy and the MCD were measured over a very large series of polysomnograms. The levels of kurtosis and skewness were shown acceptable and a close association between expected and observed values was shown on the Q-Q plots. This was also true for variables focusing on the number of cycles per night and taking into account the individual night duration, such as NCy/SPT, which can be considered as frequencies (number of cycles per time unit). This distribution normality was confirmed in all studied subcategories: gender, age, BMI, AHI, Present or Past Major Depressive Disorder and Beck Depression Inventory.

The traditional notion that human sleep consist almost exclusively of nights with 4 or 5 cycles of about 90 minutes is thus not a good reflection of reality, as a large fraction of all polysomnograms studied

**Table 3**
NCy normality estimates across subcategories ($n$ = 2312).

| | Subjects | $n$ | Mean | SD | Sk | Krt | Compared groups | $t$-tests $p$ | Cohen's $d$ |
|---|---|---|---|---|---|---|---|---|---|
| Whole group | All | 2,312 | 4.20 | 1.16 | 0.22 | 0.34 | | | |
| Gender | Males | 1,568 | 4.23 | 1.17 | 0.25 | 0.40 | M vs F | 0.048 | 0.08 |
| | Females | 744 | 4.13 | 1.13 | 0.14 | 0.17 | | | |
| Age | ≤25 | 128 | 4.34 | 1.13 | 0.33 | −0.01 | 18–24vs 65–83 | 0.002 | 0.37 |
| | > 25– ≤ 45 | 928 | 4.33 | 1.09 | 0.17 | 0.27 | | | |
| | > 45– ≤ 65 | 1111 | 4.11 | 1.19 | 0.25 | 0.45 | | | |
| | > 65 | 145 | 3.94 | 1.23 | 0.64 | 0.64 | | | |
| BMI | ≤20 | 114 | 4.25 | 1.11 | 0.29 | −0.10 | ≤20vs > 40 | 0.001 | 0.46 |
| | > 20 – ≤ 30 | 1464 | 4.28 | 1.14 | 0.17 | 0.18 | | | |
| | > 30 – ≤ 40 | 646 | 4.06 | 1.17 | 0.41 | 0.85 | | | |
| | > 40 | 88 | 3.72 | 1.17 | −0.12 | 0.017 | | | |
| AHI | ≤10 | 1912 | 4.25 | 1.29 | 0.23 | 0.28 | ≤10vs > 30 | 0.001 | 0.33 |
| | > 10 – ≤ 20 | 125 | 4.20 | 1.31 | 0.29 | 1.27 | | | |
| | > 20 – ≤ 30 | 86 | 3.96 | 1.17 | 0.29 | −0.11 | | | |
| | > 30 | 189 | 3.83 | 1.25 | .33 | 0.26 | | | |
| PLMI | ≤20 | 1.938 | 4.24 | 1.14 | .21 | .34 | ≤20vs > 60 | 0.001 | 0.87 |
| | > 20 – ≤ 40 | 279 | 4.10 | 1.20 | 0.37 | 0.33 | | | |
| | > 40 – ≤ 60 | 68 | 3.76 | 1.19 | 0.52 | 1.54 | | | |
| | > 60 | 27 | 3.22 | 1.19 | 0.13 | 0.09 | | | |
| BDI | ≤4 | 1,284 | 4.23 | 1.18 | 0.24 | 0.33 | ≤ 4vs > 16 | 0.516 | 0.08 |
| | > 4 – ≤ 8 | 326 | 4.16 | 1.10 | 0.13 | −0.31 | | | |
| | > 8 – ≤ 16 | 279 | 4.24 | 1.12 | 0.15 | 0.66 | | | |
| | > 16 | 73 | 4.14 | 1.00 | 0.56 | 0.72 | | | |
| MDD | + | 475 | 4.20 | 1.20 | 0.27 | 0.35 | (+) vs (−) | 0.911 | 0.01 |
| | – | 1,837 | 4.20 | 1.15 | 0.21 | 0.34 | | | |
| Caffeine | + | 1,716 | 4.18 | 1.15 | n.a. | n.a. | (+) vs (−) | 0.216 | 0.06 |
| | – | 596 | 4.25 | 1.19 | n.a. | n.a. | | | |
| Alcohol | + | 528 | 4.15 | 1.15 | n.a. | n.a. | (+) vs (−) | 0.226 | 0.06 |
| | – | 1,784 | 4.22 | 1.17 | n.a. | n.a. | | | |
| Tobacco | + | 497 | 4.03 | 1.14 | n.a. | n.a. | (+) vs (−) | 0.001 | 0.02 |
| | – | 1,815 | 4.25 | 1.16 | n.a. | n.a. | | | |
| REM-L | SOREMP | 55 | 5.31 | 1.19 | 0.77 | 0.78 | Short- vs Long | 0.001 | 1.46 |
| | Short REM-L | 736 | 4.67 | 1.07 | 0.45 | 0.48 | | | |
| | Average REM-L | 1,163 | 4.16 | 1.01 | 0.28 | − 0.08 | | | |
| | Long REM-L | 347 | 3.15 | 1.04 | 0.22 | 0.04 | | | |

Legend: All the numbers reported are for NCy (Number of Cycles); S.D., Standard deviation; Sk, skewness; Krt, Kurtosis; BMI, Body mass index; AHI, Apnea-hypopnea Index. MDD, Present or past major depressive episode. BDI, Beck depression inventory. REM-L, REM latency (11 missing values); Excellent degrees of skewness and kurtosis were observed in all cases. Compared groups, whole groups or binary division between the extremes to maximize differences. The variables on the *top panel* could potentially influence the NCy. The REM-L data on the *bottom panel* are provided for descriptive reasons only.

here showed less cycles, and a substantial fraction included more cycles. The MCD, usually thought to last about 90 minutes, also followed a rather wide distribution. The NCy and the MCD should thus be considered as normally distributed biological variables. They can thus be entered in parametrical comparisons. In species displaying a lot more cycles per 24 h, such as mice (Le Bon et al., 2007) and rats (Le Bon et al., 2009), normal distributions were also found.

As the normality of the distribution was confirmed, it was possible to explore the strength of links between NCy, NCy/SPT and MCD, and other sleep variables, which was the second objective of the present paper.

The NCy was shown to be strongly linked to sleep duration variables

**Table 4**
Correlations between the NCy and selected sleep and clinical variables.

| | NCy | NCy/SPT | MCD | Age | TIB | SPT | TST | NREM | N3 | REM | REM/NREM | BDI | AHI | ESS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NCy/SPT (frequency) | 0.888 | | | | | | | | | | | | | |
| MCD (min) | −0.773 | −0.868 | | | | | | | | | | | | |
| TIB (min) | 0.380 | | | | | | | | | | | | | |
| SPT (min) | 0.472 | | | | 0.831 | | | | | | | | | |
| TST (min) | 0.518 | 0.213 | −0.238 | −0.314 | 0.581 | 0.743 | | | | | | | | |
| NREM (min) | 0.405 | | | −0.263 | 0.537 | 0.709 | 0.904 | | | | | | | |
| N3 (min) | | | | −0.478 | | | 0.273 | 0.268 | | | | | | |
| REM (min) | 0.452 | 0.298 | −0.331 | −0.243 | 0.360 | 0.421 | 0.656 | 0.270 | | | | | | |
| REM/NREM (ratio) | 0.265 | 0.253 | −0.283 | | | | 0.244 | | | 0.880 | | | | |
| REM-L (min) | −0.484 | −0.581 | 0.645 | | | | | | | −0.322 | −0.357 | | | |
| AHI (events/hr) | | | | 0.260 | | | | | −0.256 | −0.243 | | | | |
| BMI (ratio) | | | | | | | | | | | | | 0.346 | |
| PLMI (score) | | | | | | | | | −0.200 | | | | 0.223 | |
| ISI (score) | | | | | | | | | | | | 0.447 | | 0.218 |

Legend: All the numbers reported are Pearsons' "$r$". NCy, Number of ultradian NREM/REM cycles; NCy/SPT, NCy*100/SPT; BMI, Body mass index; AHI, Apnea-hypopnea index; TST, Total sleep time; SPT, Sleep period time; TIB, Time in bed; N3, NREM stage 3; REM/NREM, ratio between total REMS and total NREMS in a night; REM-L, REMS Latency; BDI, Beck depression inventory (short version).;PLMI, Periodic limb movement index; ISI, Insomnia severity index; ESS, Epworth sleepiness scale. For ease of reading, correlations with Pearsons' "$r$" smaller than 200 were not shown; columns and lines with no "$r$" superior to 200 were suppressed.

**Table 5**
Comparison of demographic and sleep-related variables as a function of MDD (past or present).

| | Past or Present MDD + | | Past or Present MDD - | | F | p | Cohen's d |
|---|---|---|---|---|---|---|---|
| | N = 445° | | N = 1735° | | Univariate | | |
| | Mean | SD | Mean | SD | | | |
| Age (years) | 45.32 | 12.65 | 45.60 | 13.03 | 0.003 | NS | |
| NCy (number) | 4.20 | 1.20 | 4.20 | 1.15 | 0.022 | NS | |
| NCy/SPT (frequency) | 0.93 | 0.23 | 0.92 | 0.22 | 0.301 | NS | |
| MCD (min) | 116.90 | 41.96 | 116.93 | 39.08 | 0.492 | NS | |
| TIB (min) | 495.55 | 58.88 | 495.24 | 50.39 | 0.308 | NS | |
| SPT (min) | 452.75 | 59.05 | 455.98 | 55.35 | 1.560 | NS | |
| TST (min) | 390.28 | 61.50 | 394.05 | 61.98 | 2.461 | NS | |
| SOL (min) | 30.19 | 26.06 | 27.37 | 24.83 | 4.64 | 0.031 | 0.11 |
| SEI (ratio) | 78.94 | 9.89 | 79.65 | 10.09 | 1.5 | NS | |
| NREM (min) | 308.27 | 47.96 | 313.26 | 48.59 | 5.686 | 0.017 | −0.01 |
| N3 (min) | 30.37 | 32.71 | 26.68 | 29.49 | 4.953 | 0.026 | 0.01 |
| REM (min) | 82.02 | 27.56 | 80.68 | 27.51 | 0.425 | NS | |
| REM/NREM (ratio) | 0.27 | 0.09 | 0.26 | 0.09 | 2.277 | NS | |
| REM-L (min) | 81.56 | 47.90 | 82.22 | 46.88 | 0.359 | NS | |
| BDI (score) | 7.43 | 5.89 | 3.61 | 3.82 | 267.537 | .000 | 1.02 |
| AHI (events/hr) | 8.21 | 14.57 | 12.23 | 18.75 | 16.660 | .000 | −0.02 |
| BMI (ratio) | 26.72 | 5.71 | 28.27 | 5.95 | 24.674 | .000 | −0.02 |
| PLMI (score) | 11.54 | 12.83 | 11.17 | 12.79 | .444 | NS | |
| ESS (score) | 9.90 | 4.94 | 9.23 | 4.90 | 6.787 | 0.009 | 0.01 |
| ISI (score) | 15.66 | 5.69 | 12.18 | 5.99 | 114.597 | .000 | 0.59 |

Legend : : missing data ($n$ = 132, all included). Past or Present MDD: Past or present Major Depressive Disorder. NCy/SPT: Number of cycles over Sleep Period Time; MCD: Mean Cycle Duration; TIB: Time In Bed; SPT: Sleep Period Time; TST: Total Sleep Time; SOL: Sleep Onset Latency; SEI: Sleep Efficiency Index; NREM: Non-Rapid-Eye Movement Sleep; N3: NREM stage 3; REM: Rapid Eye-Movement Sleep; REM/NREM: REM over NREM ratio; REM-L: REM latency; BDI: Beck Depression Index; AHI: Apnea-Hypopnea Index; BMI: Body Mass Index; PLMI: Periodic Limb Movement Index; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index.

(TIB, SPT, TST), NREM, REM, the REM/NREM ratio and the REM-L (see below for more on REM-L). Comparing the correlations between the NCy and variables including sleep duration variables such as NCy/SPT provided interesting contrasts. For instance, the correlation with NREM was far more reduced than with REM. The REM/NREM ratio was not modified in a large measure. Links with the REM-L were stronger ($r = -0.484$ vs $-0.581$). Similar pictures were observed using MCD (Table 4). Once sleep duration variables are taken into account, these data support stronger relationships between the cycling and REM-related than NREM-related variables.

A discussion on the theories and models on sleep ultradian alternation would bring us too far here (see Le Bon, 2012). But there is one basic issue that needs clarification and where frequencies and durations of cycles can help: what is the degree of interdependence between REM and NREM within the night? As healthy adult sleep always begins with NREM sleep, we can induce that the first REM episode at least is somehow dependent on the duration/intensity of the first NREM episode for its expression. But data are not conclusive as to which measure the return of NREM after the REM episodes is dependent on the preceding REM duration/intensity. The study of cycles could either show that both states vary together in frequency and duration, which would favor a unified function of sleep. Or it could show a relative independence, in which case the two states would represent (at least) two separate functions.

In the first scenario, the duration of a REM episode determines the duration of the next NREM, hence the ratio between REM and NREM duration is more or less fixed. The main role of REM is to rejuvenate NREM in order to prolong sleep (Benington and Heller, 1994a, 1994b). Very low correlation ratios should be observed between the REM/NREM ratio and the NCy, since the number of alternations would just tell us how many times this rejuvenation process happened during the night. In the second scenario, REM and NREM obey to distinct rules as a function of distinct pressures resulting from daytime activities, and would compete for space. If there is a link between either REM or NREM and the NCy, then we can postulate that the cycling is linked preferentially to this particular state, which would hence probably play a leading role in it. A positive link between the REM/NREM ratio and NCy would favor theories in which REM sleep is the central tenet of the alternation. A negative link would favor NREM sleep being at the center of the alternation process. As we have seen above, the positive link found here between the NCy and the REM/NREM ratio tend to indicate a relative independence between the sleep states and favor theories where REM sleep is the key to the alternation. It could mean for instance that more REM sleep pressure in a night compels the system to use more cycles, perhaps because for some reason cycle duration is limited in time. An alternative explanation would be that ultradian cycles depend on a more general cyclicity carrying more REM sleep with it.

The third objective of the study was to analyze relationships between NCy, NCy/SPT, REM/NREM ratio, REM-L and MCD on one hand and variables measuring depression, sleepiness and insomnia on the other. Special care has been directed toward the study of the REM-L. This variable received considerable attention in psychiatric research after the demonstration that short REM-L were associated with depressive disorders (Kupfer and Foster, 1972). Subsequent studies had however shown that short REM-L lacked sensitivity and specificity (see Benca et al., 1992, for a meta-analysis). Links between the REM-L and the NCy have been described (Merica and Gaillard, 1985) and confirmed in a previous study by our group (Le Bon et al., 2001). They were again confirmed in the present study. As the REM-L could be considered an indirect reflection of the NCy, it was deemed interesting to measure the association between variables related to the ultradian cycling and depression.

Neither the REM-L, nor the NCy, the NCy/SPT, the MCD, the REM total duration, the REM/NREM ratio, nor categories as SOREMPs, Short- and Long-REM latencies were associated with the intensity of depressive symptoms (BDI) or with the DSM-IV diagnosis of Past or Present Major Depressive Episode. Relationships were observed for NREM and N3 and Past or Present Major Depressive Disorder, but with a reduced effect size and contradictory results, since there was less NREM sleep but more N3 in the Depressive disorders group than in controls. Put together, these results do not support either REM-related or NREM-related objective sleep variables as of much interest in the diagnosis or the evaluation of depression intensity. The best marker for depression was shown to be the subjective evaluation of Insomnia: ISI significantly was associated with the DSM-IV diagnosis ($p < 0.001$) and its intensity as measured by the BDI ($r = 0.447$). These links favor a general form of hyperexcitability (hyperarousal) rather than a specific deficit in sleep parameters (see Zung et al., 1964; Hubain et al., 2006; Hein et al., 2017 for a discussion).

The Apnea-Hypopnea Index was positively associated with increasing age and BMI, and negatively with stage N3 and REM sleep. The PLMI was inversely correlated with stage N3 and also with the NCy when it was broken down in categories (Table 2). It was positively associated with the AHI. Tobacco was also shown associated with a limited reduction in NCy. The ESS was associated with the ISI.

*Limitations and extensions*

Past diagnosis of Major Depressive Disorder and Present diagnosis of Major Depressive Disorder were pooled as one single variable in the present database (Past or Present Major Depressive Episode). This did not permit us to evaluate potential differences between Depression considered as a state, a scar or as a trait (see Giles et al., 1998). Also, the criteria to exclude medicated patients probably also removed a large chunk of the depressed patients, especially those with more severe depression.

The sample consisted only of patients having undergone a polysomnogram, not healthy controls. This can limit the extrapolation of our results. However, the Belgian social security system allows for a liberal use of polysomnograms, for the reason that they can help to disentangle cases at the crossroads of depression and sleep-disordered breathing. Many patients eventually turn out to present with neither of them, or at a low level. It was deemed interesting to keep all the patients in the database, since it permitted the study of relationships with several variables.

Considering the points described above, we find somewhat puzzling that the study of the frequency and duration of ultradian cycles has so far attracted so little interest among sleep researchers. We find it hard to imagine that only minor physiological differences would exist between a night with two cycles and a night with six.

Replications would be welcome: very few studies in the sleep literature have been specifically focused on the number of cycles or their duration, and most were performed by our group, both on humans and rodents. As such, they would surely gain in credibility, were they replicated by other research teams. Using the four traditional methods of Description, Deprivation, Stimulation and Correlation, here are a few paths that could be explored from here. The description could still be enhanced. For instance, relative intra-class stability over four nights was described (Le Bon et al., 2001), and it could be interesting to check this stability over months or years. Second, cycles in a night are usually not regularly interspersed, as there are for instance commonly more cycles at the end than at the beginnings of nights. The relationship is thus not linear: what is the dynamical evolution of the REM to NREM interaction across the night? Since a shorter REM-L was correlated with a higher REM/NREM ratio, there could for instance be less NREM in the first cycle only, followed by regular REM/NREM alternation in the rest of the night. This in turn would be more supportive of hypotheses where both REM and NREM states - minus the first cycle - vary together in frequency and duration. Third, future work may also need to examine the stage of the illness, from two points of view. The timing of the PSG relative to onset of the current episode of depression may be a factor determining the pattern of sleep. Also, the age of the patient, and chronicity of depression, may affect the relationship between mood and the REM measures. Fourth, REM-specific deprivations by mechanical external interventions or by the use of monoamine oxidase inhibitors (MAOIs) would help to understand what happens to the cycling when the REM/NREM ratio is reduced (Landolt et al., 2001) or after it has rebounded (stimulation). Correlations could be tested between the NCy/MCD and a broad range of physiological and psychological variables.

This study on a large group of patients showed: 1) normal distributions across subjects of numbers of sleep cycles per night and of their mean durations; 2) both of these measures were strongly related to REM-L, REM sleep duration, and the REM/NREM sleep ratio. As opposed to a hypothesis that delta sleep determines cycle patterns, this data gives firm support to the dominance of REM-related events as a major influence on sleep cycle behaviors; 3) sleep-deprived apneics or patients suffering from PLMD were well differentiated from patients with depressive symptoms; 4) The study does not support the prevalent notion that altered REM is associated with depression.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.141.

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