Communication

Dissipation of Motor Sleep Inertia and Motor Wake Inertia in Early Relapsing–Remitting Multiple Sclerosis

Lorenzo Tonetti [1], **Federico Camilli** [2,3], **Sara Giovagnoli** [1], **Alessandra Lugaresi** [2,3] and **Vincenzo Natale** [1,*]

1 Department of Psychology "Renzo Canestrari", University of Bologna, 40127 Bologna, Italy; lorenzo.tonetti2@unibo.it (L.T.); sara.giovagnoli@unibo.it (S.G.)

2 Dipartimento di Scienze Biomediche e Neuromotorie, University of Bologna, 40139 Bologna, Italy; federico.camilli2@unibo.it (F.C.); alessandra.lugaresi@unibo.it (A.L.)

3 IRCCS Istituto delle Scienze Neurologiche di Bologna, UOSI Riabilitazione Sclerosi Multipla, 40139 Bologna, Italy

* Correspondence: vincenzo.natale@unibo.it; Tel.: +39-051-209-1816; Fax: +39-051-243-086

Abstract: While previous studies have described the time course of the dissipation of motor sleep inertia (around 70 min after wake-up time) and motor wake inertia (around 20 min after bedtime) in healthy controls (HCs), the corresponding knowledge for persons with early relapsing–remitting multiple sclerosis (RRMS) is lacking. To fill in this knowledge gap, we carried out a secondary analysis of previously collected data in 35 persons (24 females; mean age = 31.51 ± 7.74 years) with early relapsing–remitting multiple sclerosis (RRMS) and 35 (24 females; mean age = 31.29 ± 8.02) healthy controls (HCs). Each participant wore an actigraphic Micro Motionlogger Watch (Ambulatory Monitoring, Ardlsey, NY, USA) for seven consecutive days. The Functional Linear Modeling statistical framework was adopted to compare the dissipation of motor sleep inertia as well as motor wake inertia between RRMS and HC. As regards motor sleep inertia, no significant differences in motor activity were observed in the first 70 min after the wake-up time; however, with reference to motor wake inertia, the motor activity of RRMS persons was significantly higher than HCs in approximately the first 30 min after bedtime. Despite the small sample size, this pattern of results suggests that the dissipation of motor wake inertia is only slower in persons with RRMS as opposed to HCs.

Keywords: multiple sclerosis; actigraphy; motor activity; sleep inertia; wake inertia; dissipation

1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS), both chronic and autoimmune, with high heterogeneity in symptomatology according to the damaged area of the CNS as well as an unpredictable course at onset. The most common form of MS at onset is the relapsing remitting (RRMS) type.

In recent years, the motor activity profile over 24 h of early (less than 24 months from diagnosis) RRMS has been described [1], with higher motor activity in patients than healthy controls (HCs) at 05:00 a.m. This datum has been interpreted on the basis of hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis and the subsequent higher cortisol awakening response previously observed in RRMS [2].

Even more recently, the first studies on the time course of motor sleep inertia [3] and motor wake inertia [4] dissipation in healthy controls have been published. Sleep inertia can be defined as a "transitional state between sleep and wake, marked by impaired performance, reduced vigilance, and a desire to return to sleep" [5] (p. 76). It was shown [3] that motor sleep inertia dissipation, ecologically assessed through the recording of motor activity with actigraphy, is completed in 70 min. Later [4], the dissipation of motor wake inertia was also examined, namely, the motor activity pattern in the transition between wakefulness and sleep that is completed around 20 min after bedtime.

To the best of our knowledge, the time course of motor sleep inertia and motor wake inertia dissipation, ecologically assessed through actigraphy, has not yet been investigated in persons with MS. Since sleep seems to be altered in MS [6], although data reported in the literature are not completely homogeneous, with the aim to better understand the relationship between sleep and MS it could be interesting to examine the times of transitions between sleep and wakefulness, as well as vice versa, that, until now, have not yet been explored. Therefore, the aim of this secondary analysis of previously collected data [1] is to fill in this knowledge gap by re-examining the data of persons with early RRMS in comparison with HCs matched by gender and age. Considering the disease condition, we could expect that RRMS patients might show higher difficulty in the transition between sleeping and waking, as well as vice versa, compared to HCs.

2. Materials and Methods

2.1. Participants

An overall number of 35 persons with early RRMS (24 females) and 35 HCs (24 females) were enrolled in the original study [1]. The gender was perfectly balanced between groups ($\chi^2_1 = 0$; $p = 1$) and age was far from significance, with the mean age of the RRMS persons equal to 31.51 years (standard deviation = 7.74) while that of the HCs was 31.29 years (standard deviation = 8.02) ($t_{68} = 0.12$; $p = 0.90$).

The inclusion criteria of both early RRMS persons and HCs were fully reported in the original study [1]. Among those criteria, we can recall here for the early RRMS persons the following: no more than 24 months from the diagnosis, no relapse or steroid treatment in the last month and absence of disability interfering with motor activity. As regards the HCs, we can quote the absence of sleep disorders and disability interfering with motor activity as well as no use of psychoactive drugs.

2.2. Actigraphy

The actigraph Micro Motionlogger Watch, commercialized by Ambulatory Monitoring Inc. (Ardlsey, NY, USA), was used for the present study. Ambulatory Monitoring Inc. (Ardsley, NY, USA) was among the first companies to introduce commercially available actigraphs more than 35 years ago [7,8]. The actigraph is a widely used device for prolonged monitoring of the sleep/wake pattern in a person's natural environment [9,10], which achieves resounding success [11,12].

The device used in this study is equipped with a triaxial accelerometer, presenting a sensitivity equal to 0.01 g, and a sampling frequency of 32 Hz, while filters are set at 2–3 Hz. The Motionlogger Watchware software (version 1.99.34.1; Ambulatory Monitoring, Inc., Ardlsey, NY, USA) was used to initialize the actigraphs in zero crossing mode to collect motor activity counts in 1 min epochs.

2.3. Motor Sleep Inertia and Motor Wake Inertia

To explore the time course of motor sleep inertia, Action 4 software (version 1.16; Ambulatory Monitoring, Inc., Ardlsey, NY, USA) was used to extract the motor activity counts, minute-by-minute, between 120 min before and 120 min after the wake-up time (i.e., the time of day that participants got out of bed).

In the same way, to analyze the time course of motor wake inertia, we extracted the motor activity counts, minute-by-minute, between 120 min before and 120 min after bedtime (i.e., the time of day that participants went to bed trying to fall asleep).

2.4. Procedure

Participants wore the actigraph around the non-dominant wrist 24 h per day for an overall number of seven consecutive days [13] and filled in a sleep diary [14]. Moreover, they were requested to push the event-marker button of the actigraph to indicate the bedtime and wake-up time. If participants forgot to push the event-marker button, the scorer referred to the sleep diary to check the bedtime and wake-up time.

This study was conducted in accordance with the Declaration of Helsinki, and approved by the Bologna-Imola Ethics Committee (protocol number 0122151 of 18 October 2017).

2.5. Statistical Analyses

Functional Linear Modeling (FLM) [15] was adopted in the present study and performed through the "actigraphy" package in the statistical software R (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/ accessed on 19 December 2023). We used FLM because it was specifically developed to analyze the actigraphy data with advanced statistical techniques as well as to facilitate the comparison between the current data with those previously reported/examined in the literature with the same statistical framework. More specifically, the time course of motor sleep inertia and motor wake inertia between RRMS persons and HCs was compared through a between-subjects FLM comparison. As shown in Figures 1 and 2, the upper part of the FLM plot shows the functional forms of the motor activity profile at the transition between sleeping and waking (Figure 1) and vice versa (Figure 2), while the lower part shows the results of the non-parametric permutation F-test. Significant differences are detected when the red solid line (i.e., the observed statistics) is higher than both the blue dashed (i.e., the global test of significance with alpha set at $p < 0.05$) and dotted (i.e., the pointwise test of significance with alpha set at $p < 0.05$) lines.
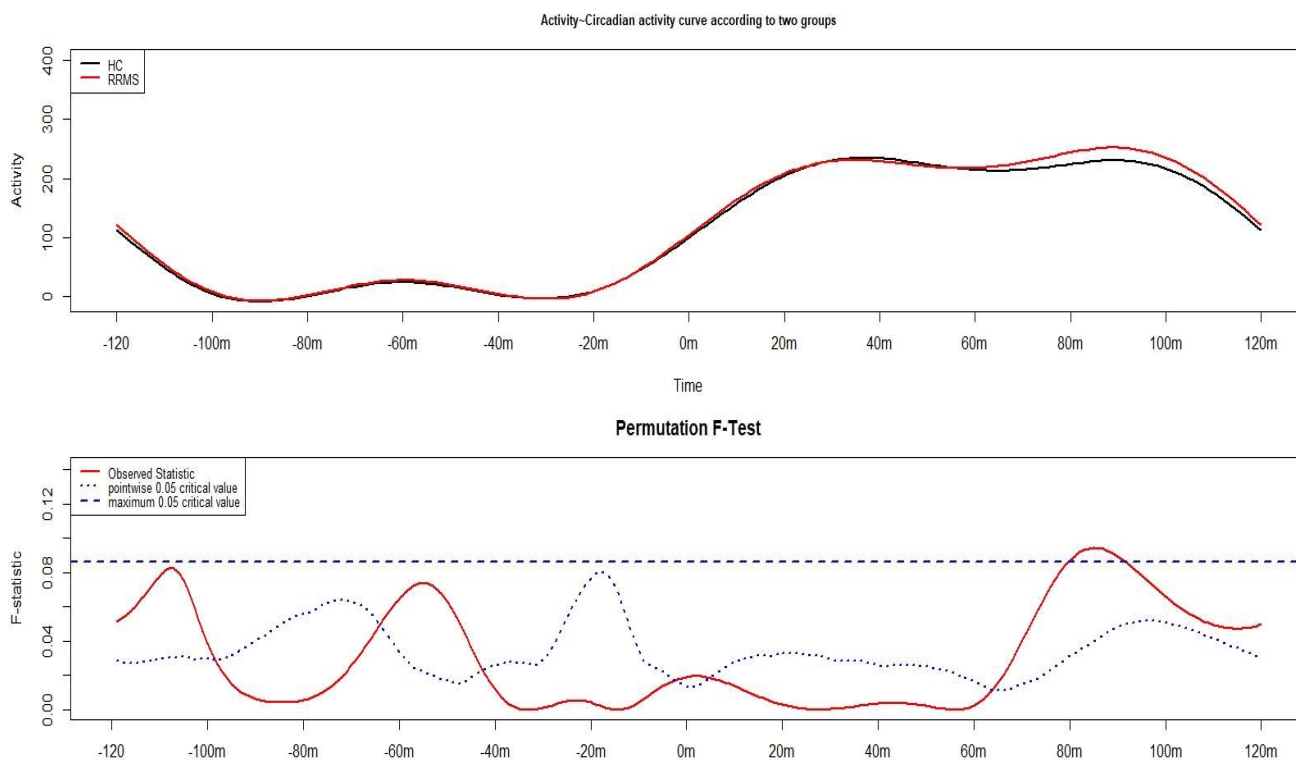
Figure 1. FLM plot related to the profile of the sleep–wake transition in RRMS persons and HCs.
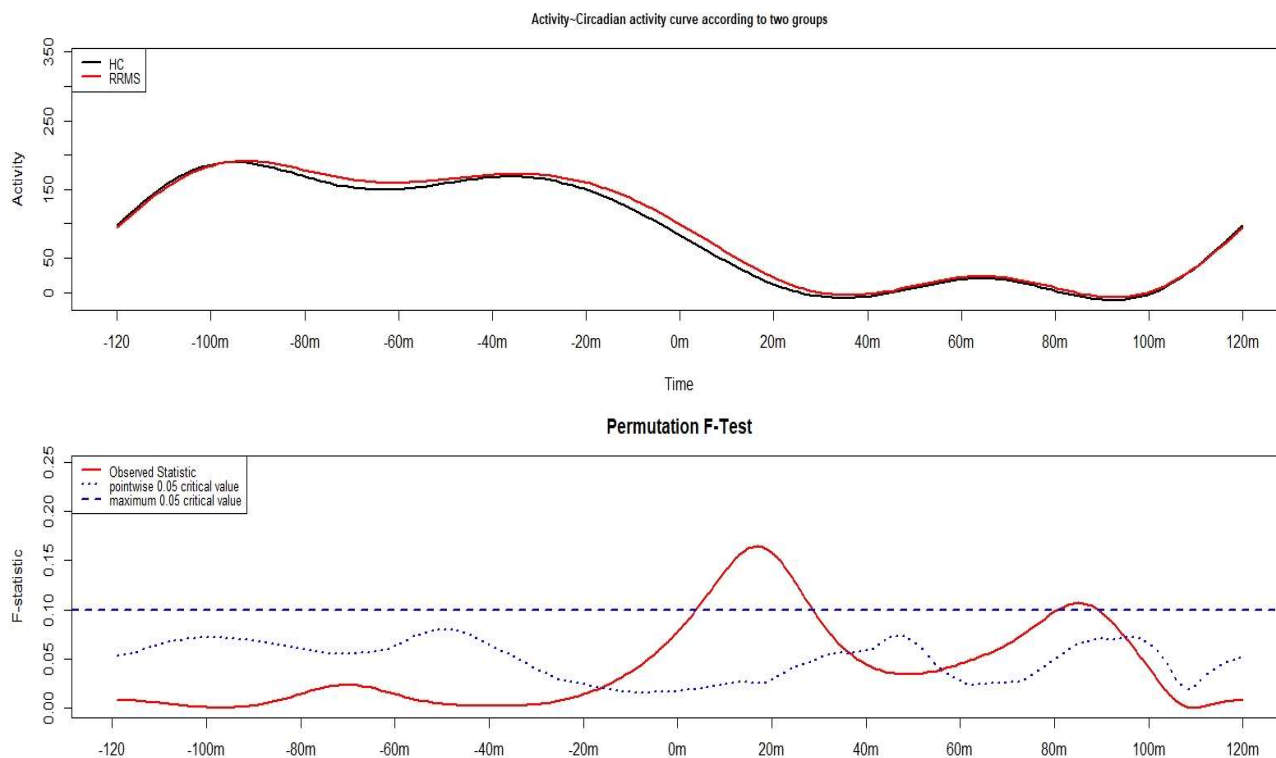
Figure 2. Results of the FLM analysis applied to the breakdown of the wake–sleep transition in RRMS persons and HCs.

3. Results

3.1. Time Course of Motor Sleep Inertia

The FLM highlighted a single time interval with significant differences between the motor activity of the groups. Specifically, between 80 and 90 min after the wake-up time, the motor activity of RRMS persons was significantly higher than the motor activity of HCs (Figure 1).

3.2. Time Course of Motor Wake Inertia

The between-subjects FLM pointed out two time intervals, both after bedtime, with significant differences between groups, i.e., between a few minutes after bedtime up to almost 30 min after it, as well as around 85 min after bedtime, with higher motor activity in the RRMS persons (Figure 2).

4. Discussion

The aim of this secondary analysis of previously collected data [1] was to shed light, for the first time, on the time course of motor sleep inertia and motor wake inertia dissipation in persons with early RRMS compared with HCs.

As regards the time course of motor sleep inertia dissipation, the unique time interval with significant differences in motor activity between groups has been observed around 80–90 min after the wake-up time, with higher motor activity in early RRMS persons. Since this difference occurs later than the time taken by motor sleep inertia to dissipate in healthy controls, i.e., within 70 min from the wake-up time [3], we can conclude that motor sleep inertia dissipation is not different in patients compared to controls. A potential explanation of this result, which is not in line with our expectations, might be related to the hyperactive HPA axis in RRMS persons [2], which may mask the supposed higher difficulty of patients in the transition between sleeping and waking.

With reference to the time course of motor wake inertia dissipation, we observed higher motor activity in persons with RRMS compared to HCs between a few minutes after bedtime up to about 30 min after it. Since it has been reported that motor wake inertia dissipates in healthy controls in 20 min [4], we can infer that motor wake inertia is more marked in persons with RRMS than HCs, in line with our expectations. This pattern of results is confirmed by the longer sleep onset latency in RRMS persons than HCs [1]. Moreover, if we use the two-process model of sleep regulation [16,17] as a theoretical framework, the observed slower dissipation of motor wake inertia in RRMS persons could involve the homeostatic process more than the circadian, as previously suggested [4], potentially pointing out a lower homeostatic sleep pressure in early RRMS. A further explanation of this result might be related to the hyperactive HPA axis in RRMS persons [2], which may increase difficulty patientsin the transition between wake and sleep. This secondary explanation is not necessarily alternative to the first one.

With reference to potential implications of the present study, if the lower homeostatic sleep pressure in early RRMS is confirmed, some potential interventions could be specifically designed, for example involving early RRMS persons with low disability in physical exercise programs [18,19], which has been proven to boost the homeostatic sleep process [20].

Among the limitations of the current study, we must acknowledge the relatively small sample size. To overcome this limitation, future studies on larger samples are required. More specifically, further studies should verify the suitability of the working hypothesis on the role played by the homeostatic process in the regulation of motor wake inertia by plotting motor activity at the transition between waking and sleeping against the total amount of wakefulness. Moreover, future longitudinal studies are needed to assess whether the sleep onset issue is associated or not with the severity of the disorder in order to improve the wellbeing of these persons [21].

5. Conclusions

The aim of this secondary analysis of previously collected data was to explore the time course of motor sleep inertia and motor wake inertia dissipation in persons with early RRMS. While the dissipation of motor sleep inertia was not different between early RRMS persons and HCs, a more marked motor wake inertia was observed in early RRMS persons that, using the two-process model of sleep regulation as a theoretical framework, was interpreted as the consequence of a lower homeostatic sleep pressure. Such a pattern of results is also compatible with the hyperactive HPA axis in RRMS persons.

References

1. Tonetti, L.; Camilli, F.; Giovagnoli, S.; Natale, V.; Lugaresi, A. Circadian Activity Rhythm in Early Relapsing-Remitting Multiple Sclerosis. *J. Clin. Med.* **2019**, *8*, 2216. [CrossRef] [PubMed]
2. Kern, S.; Schultheiss, T.; Schneider, H.; Schrempf, W.; Reichmann, H.; Ziemssen, T. Circadian cortisol, depressive symptoms and neurological impairment in early multiple sclerosis. *Psychoneuroendocrinology* **2011**, *36*, 1505–1512. [CrossRef] [PubMed]
3. Tonetti, L.; Fabbri, M.; Giovagnoli, S.; Martoni, M.; Occhionero, M.; Natale, V. Time Course of Motor Sleep Inertia Dissipation According to Age. *Brain Sci.* **2022**, *12*, 424. [CrossRef] [PubMed]
4. Tonetti, L.; Occhionero, M.; Fabbri, M.; Giovagnoli, S.; Grimaldi, M.; Martoni, M.; Natale, V. Time Course of Motor Activity Wake Inertia Dissipation According to Age. *Clocks Sleep* **2022**, *4*, 381–386. [CrossRef] [PubMed]
5. Trotti, L.M. Waking up Is the Hardest Thing I Do All Day: Sleep Inertia and Sleep Drunkenness. *Sleep Med. Rev.* **2017**, *35*, 76–84. [CrossRef] [PubMed]
6. Zhang, Y.; Ren, R.; Yang, L.; Zhang, H.; Shi, Y.; Vitiello, M.V.; Sanford, L.D.; Tang, X. Sleep in multiple sclerosis: A systematic review and meta-analysis of polysomnographic findings. *J. Clin. Sleep. Med.* **2023**, *19*, 253–265. [CrossRef] [PubMed]
7. Sadeh, A.; Sharkey, M.; Carskadon, M.A. Activity-Based Sleep-Wake Identification: An Empirical Test of Methodological Issues. *Sleep* **1994**, *17*, 201–207. [CrossRef]
8. Sadeh, A.; Alster, J.; Urbach, D.; Lavie, P. Actigraphically based automatic bedtime sleep-wake scoring: Validity and clinical applications. *J. Ambul. Monit.* **1989**, *2*, 209–216.
9. Kripke, D.F.; Mullaney, D.J.; Messin, S.; Wyborney, V.G. Wrist actigraphic measures of sleep and rhythms. *Electroen. Clin. Neurophysiol.* **1978**, *44*, 674–676. [CrossRef] [PubMed]
10. Tryon, W.W. *Activity Measurement in Psychology and Medicine*; Plenum Press: New York, NY, USA, 1991.
11. Liguori, C.; Mombelli, S.; Fernandes, M.; Zucconi, M.; Plazzi, G.; Ferini-Strambi, L.; Logroscino, G.; Mercuri, N.B.; Filardi, M. The evolving role of quantitative actigraphy in clinical sleep medicine. *Sleep Med. Rev.* **2023**, *68*, 101762. [CrossRef]
12. Smith, M.T.; McCrae, C.S.; Cheung, J.; Martin, J.L.; Harrod, C.G.; Heald, J.L.; Carden, K.A. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. *J. Clin. Sleep Med.* **2018**, *14*, 1209–1230. [CrossRef] [PubMed]
13. Briscoe, S.; Hardy, E.; Pengo, M.F.; Kosky, C.; Williams, A.J.; Hart, N.; Steier, J. Comparison of 7 versus 14 days wrist actigraphy monitoring in a sleep disorders clinic population. *Chronobiol. Int.* **2014**, *31*, 356–362. [CrossRef] [PubMed]
14. Carney, C.E.; Buysse, D.J.; Ancoli-Israel, S.; Edinger, J.D.; Krystal, A.D.; Lichstein, K.L.; Morin, C.M. The consensus sleep diary: Standardizing prospective sleep self-monitoring. *Sleep* **2012**, *35*, 287–302. [CrossRef]
15. Wang, J.; Xian, H.; Licis, A.; Deych, E.; Ding, J.; McLeland, J.; Toedebusch, C.; Li, T.; Duntley, S.; Shannon, W. Measuring the impact of apnea and obesity on circadian activity patterns using functional linear modeling of actigraphy data. *J. Circadian Rhythms* **2011**, *9*, 11. [CrossRef]
16. Borbély, A.A. A two process model of sleep regulation. *Hum. Neurobiol.* **1982**, *1*, 195–204. [PubMed]
17. Borbély, A.A.; Daan, S.; Wirz-Justice, A.; Deboer, T. The two-process model of sleep regulation: A reappraisal. *J. Sleep Res.* **2016**, *25*, 131–143. [CrossRef]
18. Bjarnadottir, O.H.; Konradsdottir, A.D.; Reynisdottir, K.; Olafsson, E. Multiple sclerosis and brief moderate exercise. A randomised study. *Mult. Scler. J.* **2007**, *13*, 776–782. [CrossRef]
19. Heesen, C.; Romberg, A.; Gold, S.; Schulz, K.-H. Physical exercise in multiple sclerosis: Supportive care or a putative disease-modifying treatment. *Expert Rev. Neurother.* **2006**, *6*, 347–355. [CrossRef] [PubMed]
20. Driver, H.S.; Taylor, S.R. Exercise and sleep. *Sleep Med. Rev.* **2000**, *4*, 387–402. [CrossRef]
21. Novak, A.M.; Lev-Ari, S. Resilience, Stress, Well-Being, and Sleep Quality in Multiple Sclerosis. *J. Clin. Med.* **2023**, *12*, 716. [CrossRef] [PubMed]