

Letters

Check for updates

Dysregulation of mood, energy, and social rhythms syndrome (DYMERS): A working hypothesis

Journal of Public Health Research 2024, Vol. 13(2), 1–5 © The Author(s) 2024 DOI: 10.1177/22799036241248022 journals.sagepub.com/home/phj



Mauro Giovanni Carta¹, Michele Fornaro², Diego Primavera¹, Antonio Egidio Nardi³ and Elie Karam⁴

Abstract

A syndrome centered on the dysregulation of behavioral rhythms (DBR) is discussed. Recent pandemic brought to observe: (1) Having a DBR affecting sleep patterns, eating habits, and social interactions, before the lockdown period, was a determinant for depressive episodes during the lockdown; (2) In tighter lockdowns, DBR triggered depressive episodes in bipolar patients; (3) DBR in healthcare workers under pressure was a determinant of burnout; (4) DBR influenced the course of chronic diseases by altering immune responses. In addition, it was found that scoring positive on the Mood Disorder Questionnaire (MDQ) was closely associated with the dysregulation of sleep rhythms. MDQ is a screening tool for bipolar disorder (BD), criticized for detecting too many false positives. Studies showed that positivity to the MDQ implied a severe impairment of quality of life even in people without psychiatric diagnoses. According to this evidence, three different hyperactivation levels could be proposed (from normality to pathology): firstly, an adaptive increase in energy (e.g. athletes performing well); secondly, a DBR determined from the continuous stimulation of stress hormones, with possible positive scores on the MDQ without a diagnosis of bipolar disorder, like in burnout syndromes and, thirdly, hyperactivity during manic episodes. The Dysregulation of Mood, Energy, and Social Rhythms Syndrome (DYMERS), the second level of the scale, is proposed as a working hypothesis. DYMERS is also seen as a vulnerable condition that may evolve in other disorders (including BD) according to the individual susceptibility (including genetic predisposition) and the specific nature/level of the stressor.

Keywords

Hyperactivation, stress, social rhythm dysregulation, biological rhythm dysregulation, mood disorder, bipolar disorder Date received: 12 February 2024; accepted: 2 April 2024

Introduction: The emergence of clinical relevance of social rhythm dysregulation at the time of COVID-19

The perturbation of sleep and biorhythms exerts significant and adverse impacts on multiple metabolic pathways. Sleep assumes a critical role in the initiation, recurrence, dysfunction, and unfavorable health outcomes associated with various mental disorders, with a particular emphasis on bipolar disorder (BD). Many factors contributes to sleep disturbances, including external environmental elements such as road traffic noise and the influence of artificial light. These external factors profoundly affect

³Laboratory Panic and Respiration, Institute of Psychiatry (IPUB), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil ⁴Institute for Development, Research, Advocacy and Applied Care (IDRAAC), Beirut, Lebanon and Department of Psychiatry and Clinical Psychology, St Georges University of Beirut, Beirut, Lebanon

Corresponding author:

Diego Primavera, Department of Medical Sciences and Public Health, University of Cagliari, Via Ospedale 54, Cagliari 09123, Italy. Email: diego.primavera@tiscali.it

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Department of Medical Sciences and Public Health, University of

²Section of Psychiatry - Department of Neuroscience, Reproductive Sciences, and Dentistry, University School of Medicine Federico II, Naples, Italy

immune-hormonal circadian timing mechanisms (24-h rhythms) and other inherent rhythms that have evolved to optimize human behavior when synchronized with light variations (for circadian rhythms) and other environmental factors like weather and seasons.^{1,2}

A hypothesis has been put forward suggesting that alterations in sleep-wake cycle rhythms³ could serve as a triggering factor for the onset of bipolar disorder. This might be attributed to the modern era's lifestyle changes, where staying awake at night could result in increased energy levels as an adaptation. However, this departure from the energy expenditure pattern established over millennia of evolution creates a disparity between current habits and the evolutionary perspective.²

During the Covid period and the related lockdowns, the clinical relevance of the dysregulation of social and behavioral rhythms came to the attention of researchers and clinicians. During that terrible "quasi-experimental condition," induced by the need to counter the pandemic, the following evidence emerged:

- (1) The dysregulation of the rhythms before the lockdown was a predictor of depressive risk and of the low level of quality of life in the elderly during the lockdown (and, conversely, a good social rhythm was a factor of resilience)^{4,5};
- (2) The dysregulation of rhythms induced by a strict form of lockdown was a potent trigger of depressive episodes in people with bipolar disorder, when compared to people with the same disorder, but not under such a strict lockdown. Even if it is probable that the same risk occurred in relation to episodes of mania, no evidence is available, in the published research as it was not possible to investigate this aspect, given the rarer occurrence of manic episodes and the consequent need for larger sample sizes to verify this hypothesis⁶;
- (3) The hyperactivation and burnout syndromes induced in healthcare professionals under stress and with alterations in social rhythms (i.e. not leaving the hospital for weeks for fear of infecting family members while experiencing the horror of death from Covid and the fear of getting infected)^{7–11};
- (4) The disruption of social rhythms influences the course of chronic diseases through the disruption of biorhythms and the modifications of the immune response. 12,13

Hyperactivation and stress: The risk of short-circuit

Having to face a serious prolonged difficulty leads to the activation of the chronic stress response. ^{14,15} It is well known that, at times when greater efforts are required by

the body, cortisol causes an increase in blood sugar and fat in the blood. 16 In this way, the body has more energy available for a prompt response. The combination of cortisol and catecholamines raises blood pressure to improve physical performance and alertness. Tension leads to less sleep and sleep restriction, with the consequent light hyperstimulation, induces, through melatonin, an imbalance of stimulating sex hormones (estradiol and testosterone) toward the stabilizing ones (progesterone and derivatives). 17 This recruitment of additional energy can have an adaptive effect, that is, it can allow unusual difficulties to be overcome. However, even in people without a predisposition to pathological mood cyclicity, continuous stimulation by stress, especially when the issues producing stress are not solved and persist, can cause hyperactivity, irritability, sleep disturbances, and disruption of social and behavioral rhythms. 18 In people with specific predispositions, activation of cortisol and neuro-stimulating steroids (summarizing the effect of the decrease in sleep and the consequent light pollution that leads to melatonin dysregulation) is associated with the risk of mania. 19,20 In fact, people with bipolar disorders showed higher levels of testosterone and estradiol during manic episodes. 18,21

Dysregulation of mood, energy, and social rhythms syndrome a common stress-related disorder?

It is possible to suppose that the dysregulation of social and behavioral rhythms could be a basis of common vulnerability from which different pathological pictures could develop according to the specific individual vulnerability.

The Mood Disorder Questionnaire (MDQ) is an instrument that was initially conceived as a screening test for hypomania and that consists of 13 questions, which aim to detect a state of hyperarousal and hyper-energy.^{22–24} However, people that did not receive a diagnosis of bipolar disorder during clinical investigations, and people with psychiatric diagnoses other than bipolar disorder, frequently scored positive on this tool, thus its accuracy was debated.^{25,26}

Some researchers interpreted these high numbers of "false positives" as the fact that the diagnoses of bipolar disorder did not cover the whole "spectrum" of disorders, but only the tip of the iceberg and therefore only the most serious cases.²⁷ In fact, there was a strong evidence of comorbidity between bipolar disorders and almost all the pathologies highlighted in the "false positives." It is also well known that when another mental health condition shows comorbidity with bipolar disorder, frequently the onset of bipolar disorder has followed the onset of the other disorder ever by years.^{28,29} The false positives could, therefore, be subthreshold cases that would have eventually led to a diagnosis of bipolar disorder several years after the evaluation.

Carta et al. 3

However, new data has ascertained that:

- (1) Positive scores on the MDQ are closely associated with the dysregulation of sleep rhythms.³⁰ The rhythm of sleep is, in turn, closely linked with the rhythms of eating and socializing.³¹ Positive scores on the MDQ, therefore, reveal a syndrome characterized by hyperactivity (which is not always sufficient to identify an episode of hypomania) with dysregulation of social and behavioral rhythms.
- (2) Positive scores on the MDQ are associated with a serious impairment of the quality of life, similar, in terms of importance, to that highlighted in serious chronic diseases, but independent of the presence of mood disorders⁸ or other psychiatric diagnoses.³² This impairment in quality of life in MDQ-positive people is independent of comorbidity and comes evident even at an old age, when a late onset of another psychiatric diagnosis is possible, but unlikely.³³

This new data, therefore, suggests that the "false positives" at the MDQ could reveal a "sui generis" spectrum of mental suffering, characterized by the hyperactivation and the dysregulation of social and personal rhythms, independent of other psychiatric disorders. However, it may be considered a common risk that would develop in different ways based on the different individual vulnerabilities (including genetic ones) and the specificity of the stress that triggered the dysregulation.

As far as bipolar disorder is concerned, it must be considered that studies have recently shown that positive scores on the MDQ are not associated, "per se," with a genetic risk for this disorder.³⁰ On the other hand, one of the genetic variants found to be associated with bipolar disorder, CACNA1C rs1006737, was highly frequent in hyperactive, socially well adapted old adults without BD, to an equal extent as old adults with a diagnosis of BD, while non-hyperactive old adults without bipolar disorder had a strong lower frequency of this genetic variant. 34-36 A recent study showed that both a genetic test aimed to evaluate the presence of the genetic variant CACNA1C rs1006737, and the MDQ, could be quite accurate in screening bipolar disorder, but with unreliable and strongly specular results.³⁷ In fact, the genetic test showed a quite good sensitivity (a positive result was associated with a high probability of having bipolar disorder), whereas the MDQ was strongly specific (a negative result was associated with a high probability of not having bipolar disorder).³⁷ The unreliability of the two screening tests suggested that they do not measure the same underlying dimension of BD. This study, thus, seems to suggest the hypothesis that a condition of hyperactivation common to a stress condition, identified by a positive score on the MDO, can trigger BD in people with a predisposition to hyperactivity (i.e. people with a specific genetic predisposition).

Adaptive and non-adaptive hyperactivation

Based on what has been previously illustrated, three levels of hyperactivation can be highlighted, ranging from an adaptive response to a mental distress (a trigger condition for several mental disorders) and then to a frank mental disorder:

- (1) Adaptive increase in energy, which can be typical of any person preparing to face a difficult task, but which can lead to success. In highly trained people, the increase in adaptive energy can be marked such as in some sports stars, who report performing excellently even if they do not sleep the day before the race or the exercise due to hyper-activation.³⁸
- (2) Increase in energy linked to the dis-stress and associated with the dysregulation of social rhythms (sleep, eating, and relational),³⁹ typical of conditions in which the stress is strong and persists for a long time. In these cases, the increase in energy is still focused on the goal/issue producing the stress, but it is ineffective in resolving it, such as in occupational burnout syndromes, when some people report feeling "like a car that has its wheels spinning in the sand." The fact that stress syndromes result in false positives at the MDQ^{30,40,41} may be the consequence of the activation symptoms that accompany stress syndromes. 42 In fact, the more the hyperactivation increases, the more it negatively reverberates on the physical and mental state and the situation seems unsolvable⁴³ and it may impair the health-related quality of life. 43 Burnout/ occupational syndromes⁴³ and adjustment disorders,44 in fact, severely impair the health-related quality of life.
- (3) Hyperactivity and increased energy in the picture of an episode of hypomania or mania. In mania or hypomania, hyperactivation is out of control and loses relationships with adaptive goals (on the other hand, the hyperactivation due to stress and burnout, as described in point 2, is always focused on overcoming the issues even if it fails in its intent). In mania and hypomania, hyperactivity often rebounds into depression. For this condition to occur, stress and environmental factors need to be, possibly, associated with a specific and additional genetic risk. As indicated above, some genetic risks for bipolar disorder and a positive score on the MDQ could be independent components of BD.³⁷ A predisposition to hyperactivity could be the substrate of the disorder if trigged by great stress.

Future perspectives and tasks

At present, the diagnostic concept of "Dysregulation of Mood, Energy, and Social Rhythms Syndrome (DYMERS)" is to be considered a heuristic hypothesis, although based on different evidence sources that, together, represent stimulating clues.

It is therefore essential to verify these indications through:

- Studies on large samples, including non-clinical ones, which would allow us to verify the links between hyperactivation, dysregulation of rhythms, and stress.
- (2) Research that clarifies how different expressions of genetic vulnerability can respond differently if subjected to dysregulation of biological rhythms and stress.
- (3) Studies investigating how different personological characteristics and different genetic profiles related to personality can approach/research for stressful tasks.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Research was supported by internal funds only with no evident conflict of interest.

References

- 1. Wyse CA, Biello SM and Gill JM. The bright-nights and dim-days of the urban photoperiod: implications for circadian rhythmicity, metabolism and obesity. *Ann Med* 2014; 46(5): 253–263.
- Carta MG, Preti A and Akiskal HS. Coping with the new era: noise and light pollution, hyperactivity and steroid hormones. Towards an evolutionary view of bipolar disorders. Clin Pract Epidemol Ment Health 2018; 14: 33-36.
- 3. Bedrosian TA and Nelson RJ. Timing of light exposure affects mood and brain circuits. *Transl Psychiatry* 2017; 7(1): e1017.
- 4. Primavera D, Aviles Gonzalez C, Romano F, et al. Does the response to a stressful condition in older adults with life rhythm dysregulations provide evidence of the existence of the "dysregulation of mood, energy, and social rhythms syndrome"? *Healthcare* 2023; 12: 87.
- Carta MG, Fornaro M, Minerba L, et al. Previous functional social and behavioral rhythms affect resilience to COVID-19-related stress among old adults. *J Public Health Res* 2022; 11(2): 2768.

- Carta MG, Ouali U, Perra A, et al. Living With Bipolar Disorder in the Time of Covid-19: Biorhythms During the Severe Lockdown in Cagliari, Italy, and the Moderate Lockdown in Tunis, Tunisia. Front Psychiatry 2021; 12: 634765. doi: 10.3389/fpsyt.2021.634765
- Moro MF, Calamandrei G, Poli R, et al. The Impact of the COVID-19 Pandemic on the Mental Health of Healthcare Workers in Italy: Analyzing the Role of Individual and Workplace-Level Factors in the Reopening Phase After Lockdown. Front Psychiatry 2022;13: 867080. doi: 10.3389/fpsyt.2022.867080.
- 8. Okechukwu CE, Griffiths MD, Carta MG, et al. Biological and practical considerations regarding circadian rhythm and mental health relationships among nurses working night shifts: a narrative review and recommendations. *Riv Psichiatr* 2022; 57(2): 67–79.
- Carmassi C, Dell'Oste V, Bui E, et al. The interplay between acute post-traumatic stress, depressive and anxiety symptoms on healthcare workers functioning during the COVID-19 emergency: a multicenter study comparing regions with increasing pandemic incidence. *J Affect Disord* 2022; 298(Pt A): 209–216.
- Carmassi C, Pedrinelli V, Dell'Oste V, et al. PTSD and depression in healthcare workers in the Italian epicenter of the COVID-19 outbreak. *Clin Pract Epidemol Ment Health* 2021; 17: 242–252.
- 11. Yassin A, Al-Mistarehi AH, Qarqash AA, et al. Trends in insomnia, burnout, and functional impairment among health care providers over the first year of the COVID-19 pandemic. *Clin Pract Epidemol Ment Health* 2022; 18: e174501792206200.
- 12. Hazan G, Fox C, Eiden E, et al. Effect of the COVID-19 lockdown on asthma biological rhythms. *J Biol Rhythms* 2022; 37(2): 152–163.
- Scatà C, Carandina A, Della Torre A, et al. Social isolation: a narrative review on the dangerous liaison between the autonomic nervous system and inflammation. *Life* 2023; 13(6): 1229.
- Feelisch M, Cortese-Krott M, Santolini J, et al. Systems redox biology in health and disease. EXCLI J 2022; 21: 623–646.
- Selye H. Forty years of stress research: principal remaining problems and misconceptions. *Can Med Assoc J* 1976; 115(1): 53–56.
- Esteghamati A, Morteza A, Khalilzadeh O, et al. Association of serum cortisol levels with parameters of metabolic syndrome in men and women. Clin Invest Med 2011; 34(3): 131–137.
- Liu L, Li D, Gilbert ER, et al. Effect of Monochromatic Light on Expression of Estrogen Receptor (ER) and Progesterone Receptor (PR) in Ovarian Follicles of Chicken. *PLoS One* 2015; 10(12): e0144102. doi: 10.1371/journal.pone.0144102
- Herane Vives A, De Angel V, Papadopoulos A, et al. The relationship between cortisol, stress and psychiatric illness: new insights using hair analysis. *J Psychiatr Res* 2015; 70: 38–49.
- Hardoy MC, Serra M, Carta MG, et al. Increased neuroactive steroid concentrations in women with bipolar disorder or major depressive disorder. *J Clin Psychopharmacol* 2006; 26(4): 379–384.
- 20. Carta MG, Bhat KM and Preti A. GABAergic neuroactive steroids: a new frontier in bipolar disorders? *Behav Brain Funct* 2012; 8: 61.

Carta et al. 5

 Lyu N, Zhao Q, Fu B, et al. Hormonal and inflammatory signatures of different mood episodes in bipolar disorder: a large-scale clinical study. BMC Psychiatry 2023; 23(1): 449.

- Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the mood disorder questionnaire. *Am J Psychiatr* 2000; 157: 1873–1875.
- Hardoy MC, Cadeddu M, Murru A, et al. Validation of the Italian version of the "mood disorder questionnaire" for the screening of bipolar disorders. *Clin Pract Epidemol Ment Health* 2005; 1: 8.
- 24. Ouali U, Jouini L, Zgueb Y, et al. The factor structure of the mood disorder questionnaire in Tunisian patients. *Clin Pract Epidemol Ment Health* 2020: 16(Suppl-1): 82–92.
- Zimmerman M and Galione JN. Screening for bipolar disorder with the mood disorders questionnaire: a review. *Harv Rev Psychiatry* 2011; 19: 219–228.
- Zimmerman M, Galione JN, Ruggero CJ, et al. Screening for bipolar disorder and finding borderline personality disorder. *J Clin Psychiatry* 2010; 71: 1212–1217.
- Carta MG, Colom F, Erfurth A, et al. In memory of Hagop Akiskal. Clin Pract Epidemol Ment Health 2021; 17: 48–51.
- Serra G, Koukopoulos A, De Chiara L, et al. Features preceding diagnosis of bipolar versus major depressive disorders. *J Affect Disord* 2015; 173: 134–142.
- 29. Carta MG and Angst J. Screening for bipolar disorders: a public health issue. *J Affect Disord* 2016; 205: 139–143.
- 30. Mundy J, Hübel C, Adey BN, et al. Genetic examination of the mood disorder questionnaire and its relationship with bipolar disorder. *Am J Med Genet B* 2023; 192: 147–160.
- 31. Borisenkov MF, Vetosheva VI, Kuznetsova YS, et al. Chronotype, social jetlag, and time perspective. *Chronobiol Int* 2019; 36(12): 1772–1781.
- 32. Giovanni Carta M, Kalcev G, Scano A, et al. The impact of MDQ positivity on quality of life impairment: Does it support the hypothesis of "Dysregulation of Mood, Energy, and Social Rhythms Syndrome" (DYMERS)? *J Public Health Res* 2023; 12(4): 22799036231208356. doi: 10.1177/22799036231208356
- 33. Carta MG, Kalcev G, Fornaro M, et al. Does screening for bipolar disorders identify a "dysregulation of mood, energy, and social rhythms syndrome" (DYMERS)? A heuristic working hypothesis. *J Clin Med* 2023; 12: 5162.

- 34. Carta MG, Kalcev G, Scano A, et al. Is bipolar disorder the consequence of a genetic weakness or not having correctly used a potential adaptive condition? *Brain Sci* 2022; 13(1): 16.
- Kalcev G, Cossu G, Preti A, et al. Development and validation of the questionnaire for adaptive hyperactivity and goal achievement (AHGA). Clin Pract Epidemol Ment Health 2023; 19: e174501792303281.
- 36. Kalcev G, Scano A, Orrù G, et al. Is a Genetic Variant associated with Bipolar Disorder Frequent in People without Bipolar Disorder but with Characteristics of Hyperactivity and Novelty Seeking? Clin Pract Epidemiol Ment Health 2023; 19: e174501792303280. doi: 10.2174/17450179-v19-e230419-2022-53
- 37. Carta MG, Kalcev G, Scano A, et al. Screening, genetic variants, and bipolar disorders: can useful hypotheses arise from the sum of partial failures? *Clin Pract* 2023; 13(4): 853–862.
- 38. Gaudette J. Will a bad night's sleep before a race affect performance? San Luis, AZ, RunnersConnect, Inc., 2023. https://runnersconnect.net/coach-corner/pre-race-sleep/(accessed 26 June 2023).
- de Azevedo Bringel JM, Abreu I, Muniz MMC, et al. Health professionals' chronotype association with salivary cortisol and occupational stress in neonatal intensive care units. *Int J Environ Res Public Health* 2023; 20(9): 5683.
- Paterniti S and Bisserbe JC. Factors associated with false positives in MDQ screening for bipolar disorder: insight into the construct validity of the scale. *J Affect Disord* 2018; 238: 79–86.
- Graves RE, Alim TN, Aigbogun N, et al. Diagnosing bipolar disorder in trauma exposed primary care patients. *Bipolar Disord* 2007; 9(4): 318–323.
- Karatzias T, Hyland P, Ben-Ezra M, et al. Hyperactivation and hypoactivation affective dysregulation symptoms are integral in complex posttraumatic stress disorder: Results from a nonclinical Israeli sample. Int *J Methods Psychiatr Res* 2018; 27(4): e1745. doi: 10.1002/mpr.1745
- Roy I. [Burnout syndrome: definition, typology and management]. Soins Psychiatr 2018; 39: 12–19.
- O'Donnell ML, Alkemade N, Creamer M, et al. A longitudinal study of adjustment disorder after trauma exposure. Am J Psychiatr 2016; 173(12): 1231–1238.