Journal of Huntington's Disease 12 (2023) 85–87
DOI 10.3233/JHD-239003
IOS Press

Editorial

Introduction to the Special Issue on Sleep and Circadian Rhythms in Huntington's Disease

Jenny Morton*
Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

Accepted 6 July 2023
Pre-press 15 July 2023
Published 28 July 2023

Good quality sleep and healthy diurnal rhythms are fundamental to human health and wellness, although for the most part we greatly under-appreciate the role they play in our lives. It is only when they become disordered that we pay attention. When the timing systems in the human body are desynchronized, the function of essential organs and the immune system are compromised. The consequences of disrupting circadian rhythms are easily demonstrated by a shift of a few hours in time zone. Many of us are familiar with the experience of jetlag causing disrupted sleep, altered digestion and increased vulnerability to infection. Similarly, most of us have experienced the increased irritability, sluggish thinking, and physical exhaustion that comes with a poor night's sleep. We take for granted that we will recover from such disruptions, and that they will leave no lasting effect. In fact, the reversibility of the deleterious effects of short-term disturbances of both sleep and circadian rhythms in healthy individuals is a testament to the robust pathways and homeostatic mechanisms that underpin the survival of our species.

Unfortunately, the reversibility of deleterious effects of sleep deprivation or circadian disruption is not guaranteed. Since the turn of the century there have been considerable advances in our understanding of both the physiology and the underlying mechanisms of sleep and circadian rhythms [1, 2]. At the same time, accumulating evidence suggest that long-term disruption of circadian rhythms leads to more worrying consequences, such as an increased propensity for some cancers, diabetes and heart disease [1]. Furthermore, there is emerging awareness that both sleep and circadian rhythms abnormalities are associated with neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. The critical question for the Huntington's disease (HD) field is whether or not chronically disturbed sleep and/or circadian rhythms, that are so detrimental to the neurologically normal population, have a greater impact on people whose brains are rendered vulnerable by HD. We do not know the answer to this question, and it is time that we found out.

In this Special Issue, entitled "*Sleep and circadian disorder in Huntington's Disease*", we review what is known about sleep and circadian rhythms in HD, and perhaps just as importantly, what is *not* known. The first two reviews of this Special Issue are intended as guides for readers who want a better understanding of both circadian rhythms and sleep pathways, and the mechanisms underlying their control. A clear understanding of the underlying physiology is essential if we are to understand what might go wrong, but it is not always easy to find this information in an accessible and relevant

*Correspondence to: Jenny Morton, Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK. E-mail: ajm41@cam.ac.uk.

format. Circadian time pervades every level of biological organisation, from molecules to society. In the first review, Patton and Hastings review the mammalian circadian time-keeping system [1]. They provide a broad distillation of a large and complicated field and highlight the essential physiology that is relevant to HD researchers. In particular, they describe the relationship between biological clocks and sleep. The discovery of the core molecular 'clock' machinery not only led to a revolution in our understanding of circadian rhythms, but also to realisation that many thousands of our genes are circadian-regulated. Understanding these mechanisms offers important opportunities for mitigating the consequences of circadian disruption, so prevalent in modern societies, arising not only from shift work and ageing but also from neurodegenerative disease. In the second review, Nollet, Franks and Williams detail the pathways of sleep [2]. Their review focusses on providing an understanding of sleep regulation in normal and pathological conditions and why it matters for HD. It remains unknown if sleep deterioration precedes pathogenesis (and thus represent a risk factor for the disease) or whether they only appear as a debilitating symptom of the pathophysiological alterations. Either way, these authors make the case that sleep disturbances constitute an additional burden that usually exacerbate disease outcomes.

The direct evidence for sleep and/or circadian disfunction in HD is reviewed by Saade-Lemus and Videnovic [3]. There is growing evidence from both clinical and animal model studies that sleep changes occur early in the clinical course of the disease. Difficulties with sleep initiation and maintenance that lead not only to decreased sleep efficiency but also to progressive deterioration of normal sleep architecture are recognised as symptoms of HD. Saade-Lemus and Videnovic include a useful chronological summary of sleep and/or circadian investigations conducted to date in HD patients. They point out that despite evidence of sleep and circadian abnormalities, sleep alterations remain frequently under-reported by patients and under-recognized by health professionals. This may explain why available investigations of sleep in HD patients are sparse, with small cohorts and various methodologies. Saade-Lemus and Videnovic also include recommendations for future studies in their article.

There is robust evidence for both sleep and circadian disfunction HD animal models. This is reviewed in Morton [4]. This review points out that translating what has been learned from animal models to patients is much more challenging than measuring it. There are significant practical difficulties of measuring circadian rhythms and/or sleep EEG in humans that are relatively easily overcome in preclinical studies. For example, environmental factors (e.g., light levels, timing of light periods and diet) can be controlled relatively easily in animal studies, and animals can be implanted with devices that give a direct readout of biological rhythms in a way that is not possible in humans. Nevertheless, increasingly the evidence from human studies supports the existing evidence from HD animal models that there are significant and early disturbances in biological rhythms, including sleep. The technical constraints of working with HD patients mean that it may not be possible to replicate all of the sleep- and circadian-related findings shown in animal models in HD. However, this may not be necessary. There are several low-risk interventions shown to be successful in ameliorating circadian and sleep disruption in mice that could be tested in humans. We should use the information gleaned from animal studies to point the way to advance human studies and develop relevant therapies.

The review by Owen, Barker and Voysey [5] tackles the important question of how current treatments of HD symptoms impact sleep and considers what should be done moving forward. They suggest that the fact that sleep deficits have been identified during the premanifest stage that is far-from-disease-onset argues against the idea that sleep dysfunction occurs predominantly as a result of medication or psychiatric symptoms of HD such as depression or anxiety. They address the concern that current HD treatment approaches neither consider the impact of commonly used medications on sleep, nor directly tackle sleep dysfunction. They also discuss growing evidence for a damaging 'feedforward' cycle between sleep dysfunction and neurodegeneration. Finally, they highlight the possibility that sleep disruption may directly affect neurodegenerative processes by inducing neuroinflammation or impairing sleep-dependent clearance of neurotoxic waste.

At the risk of being repetitive, it is critical to note (as highlighted in the reviews by Saade-Lemus and Videnovic [3], and Owen et al. [5]) that current HD treatment approaches neither consider the impact of commonly used medications on sleep, nor directly tackle sleep dysfunction directly. This is left to the clinician to figure out 'empirically'.

The final two articles in this Special Issue are perspective pieces. One is from Wexler [6], a family member and historian whose sister is living with

HD, the other from Rosas [7], a clinician who has spent many years treating HD patients. While it may be argued that opinions are unscientific and have no place in a scientific journal, I believe that there is a place for them, particularly if they are based on experience. If they only serve as 'levers' for prompting discussion of how sleep and circadian disturbance affect HD patients, then these articles will have earned their place.

It is clear from the articles in this Special Issue that sleep and circadian dysfunction in HD patients is an understudied, indeed neglected, field. As noted by both Saade-Lemus and Videnovic, and Owen et al, more robust studies employing objective measurements of sleep and alertness are needed. Yet a lack of study is not the only issue. The lack of recognition of the problem is a greater big barrier to progress. Sleep dysfunction in normal people is taken seriously, and it is recognized that it exacerbates a range of cognitive symptoms, including deficits in executive function, memory consolidation, attention, and processing speed, as well as affective features such as impulsivity and emotional liability. Notably, most if not all these symptoms are present in HD at some stage in the course of the disease, yet the impact of sleep dysfunction on HD patient symptoms is rarely considered. (If sleep disturbance was caused by the off-target effect of a drug, the use of that drug would come with a label warning.)

Ten years ago, I wrote an article for HD Buzz outlining the rules for a good night's sleep that might help HD patients (https://en.hdbuzz.net/120?p=x). This was based on a combination of commonsense and a distillation of factors known to caused disrupted sleep that could be controlled. In the intervening years, while there has been growing recognition of the problem, there have been few attempts to develop treatments or interventions. As Voysey and Barker point out, strong evidence exists for the efficacy of cognitive behavioural therapy intervention and sleep hygiene behavioral measures in improving sleep quality in healthy populations, yet to date, there has been no large-scale sleep intervention study in a clinical HD population. A cynic would suggest that this is because there is no profit in therapies that do not involve pharmaceuticals. An optimist would say that, given there is clear evidence from pre-clinical studies, and growing evidence from HD patients for a role of sleep and circadian dysfunction in HD, in the next few years we should see some progress. Refinements in our understanding of drugs used to treat sleep disorder in HD as well as the development of non-pharmaceutical interventions – an affordable way of alleviating suffering for at least some of the time course of this devastating disease -are necessary, and this will require systematic study. It is also clear that a better understanding of both the means of improving sleep as well as the neurophysiological mechanisms underlying the development of sleep abnormalities in pathological context will be necessary before we can improve diagnosis and develop therapeutic interventions.

This is the first time that Sleep and Circadian dysfunction in HD has been the topic for a special issue of any journal. I hope that the range of information, from the basics of circadian and sleep biology to the impact of sleep disturbance on individuals with HD will serve as a springboard for future research and that it serves to speed us towards better discovery and treatments for HD.