Circadian Rhythm Sleep Disorders

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Circadian Disruption and Psychiatric Disorders: The Importance of Entrainment

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- Circadian rhythms • Sleep regulation • Actigraphy
- Major depression • Dementia • Psychiatric illness

There is a need for more knowledge of sleep medicine to be integrated into psychiatric training and practice. Although many psychiatrists are aware that most patients have some sort of a sleep problem, these mainly are addressed separately from the primary diagnosis, with appropriate choice of sleep-promoting psychopharmacologic agents or additional treatment with benzodiazepines or newer hypnotics. Consideration of circadian rhythms and their impact on sleep–wake behavior in psychiatric disorders is still rare in psychiatric practice.

This is somewhat surprising, because observations linking rhythmic behavior and psychopathology have a long tradition in clinical psychiatric research, particularly in major depression. These observations have been reviewed comprehensively,[1–3] albeit with rather ambiguous conclusions. The precise nature of the links remains elusive, and it may be too simplistic to expect that the enormous variety of psychiatric disorders have common dysfunctions related to the biological clock. It is not only the problem of clearly defining patient groups within and among diagnoses, but also, different treatments make it difficult to define a specific circadian rhythm abnormality. It may be more the symptoms such as anxiety and depressed mood rather than the diagnosis that are related to sleep disorders. In addition, methodological issues cloud most

investigations, because masking effects of behavior and environment on the rhythms measured often have not been controlled for.

Thus, this article will not address evidence for circadian disruption as etiology. Do clock genes play a role in bipolar disorder?[4] What is the evidence for phase–delayed rhythms in winter depression?[5,6] Do different dementias have different rhythm abnormalities?[7] Rather, circadian disruption of rest–activity cycles will be considered as a clinical symptom, which leads to pragmatic use of circadian-based treatments to support re-entrainment.

Hypotheses of biological clock disorder postulate alterations in suprachiasmatic nuclei (SCN) function that may result in a low amplitude or abnormal phase of the observed circadian rhythm. Alterations in SCN function may be caused not only by malfunction of the clock per se, but by means of changes in factors that set the clock. Importantly, the SCN—and all the peripheral clocks in the brain and the rest of the body—require zeitgebers (synchronizing agents) to ensure circadian entrainment (coupling of an endogenous rhythm to an environmental oscillator with the result that both oscillations have the same frequency), internally among themselves and externally with respect to the light-dark cycle. With insufficient zeitgebers, even correctly functioning biological clocks can become

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desynchronized. This points to the important role for the major zeitgeber light, and the usefulness of melatonin, which feeds back on the SCN. Non-photic zeitgebers such as physical exercise, sleep, or food also contribute to entrainment of peripheral clocks. Social zeitgebers (eg, personal relationships, jobs, social demands) act indirectly on the SCN, because they determine the timing of meals, sleep, physical activity, and out- and indoor light exposure. In addition, the zeitgebers must impact on correct functioning receptors to be effective (eg, retinal photoreceptors for light perception).

A major tenet of chronobiology is that appropriate entrainment or synchronization to the 24-hour day–night/light–dark cycle is important for health. This may be particularly relevant to psychiatric illness.[8] Circadian malentrainment does not necessarily cause the individual psychopathology, but may perpetuate or exacerbate the clinical symptoms. In general, entrainment is not only a prerequisite for good nighttime sleep and daytime alertness, but also for adequate mood state, cognition, and neurobehavioral function.

The chronobiological strategy of attending to entrainment of patients, independent of psychiatric diagnosis, is not entirely new, because it merely reformulates the classical clinical strategy of establishing stable daily structures to support the process of clinical improvement. The primary postulate is that integrity of the circadian rest–activity cycle promotes healthy functioning in all psychiatric disorders.

Here the focus lies on the importance of well-entrained sleep–wake cycles for mental health, with examples from various diagnostic categories. The accent will be on actigraphy, as a well-established, relatively easy and noninvasive objective measure of the circadian rest–activity cycle.

ACTIGRAPHY AS A CLINICAL TOOL

Actigraphs are small, lightweight, wrist-worn solid-state recorders that record movement-induced accelerations (**Fig. 1**). The wrist-worn accelerometer generates activity counts, which are proportional to the intensity, frequency, and duration of motion (the higher the black bars, the more active). The activity counts are summed over a given time interval (eg, 2-minutes) and depicted either as single plots (24-hours) or double plots (48-hours represent day 1 and day 2 next to one another); time of day (x axis) begins at midnight. The subsequent days (y axis) are plotted beneath each another.

In general, two sets of parameters can be derived—one representing sleep measures such as sleep fragmentation and movement time, which correlate reasonably well with electroencephalogram (EEG) data[9]—and one set defining circadian rhythm characteristics, such as interdaily stability (IS), intradaily variability (IV), the timing of the most active and most inactive episodes, and the relative amplitude (RA).[10] IS indicates the degree of resemblance between activity patterns on different days, documenting the consistency across days of the daily circadian signal and the strength of its coupling to stable zeitgebers. A higher value indicates a more stable rhythm. IV indicates the degree of fragmentation of the rhythm (ie, the frequency of transitions between periods of rest and periods of activity during a given day). A lower value indicates a less fragmented rhythm. The sequence of the most active
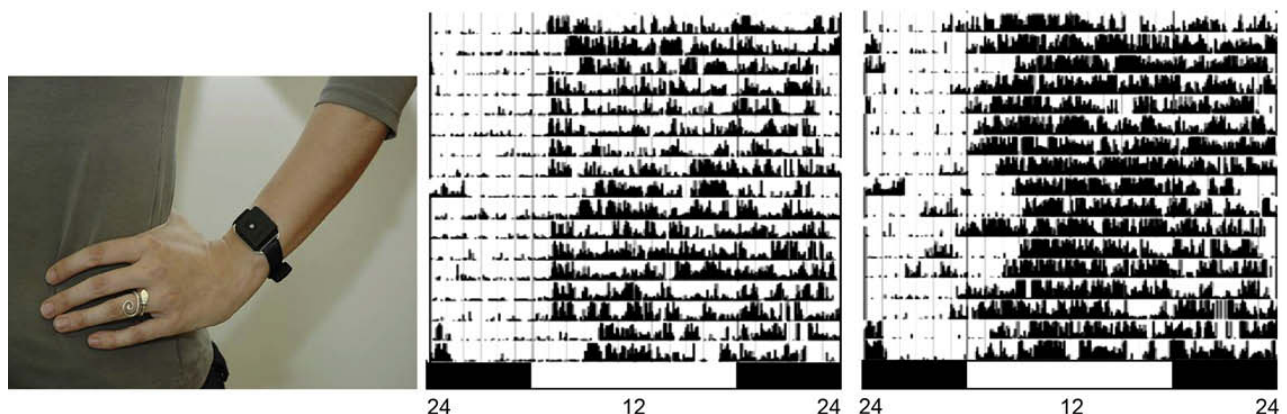

Fig. 1. The circadian rest–activity cycle is documented using an actigraph worn on the wrist of the nondominant hand (inset, Cambridge Neurotechnology Limited, Cambridge, UK, with light meter). Social zeitgebers in a married couple showing weekday work times affecting the onset of daily activity in the employed partner (63-year-old man), *left*, and free choice of wake-up time in the at-home partner (65 year-old woman), *right*. (*Data from* A. Wirz-Justice, unpublished data, 2009.)

10 hours (day) indicates the mean hourly peak of the rhythm, and the sequence of the least active 5 hours (night) indicates the nadir of the rhythm.[10] These two values are used to calculate the third important characteristic, the RA.

Many psychiatric illnesses are accompanied or characterized by changes in the circadian sleep–wake cycle. The advantage of actigraphy is to reveal 24-hour patterns that cannot be obtained otherwise, and which provide objective data for the patient's sleep disturbance. The technique is noninvasive, reliable, and can be interpreted within the paradigm of animal circadian rest–activity cycles, where a large literature can be invoked to interpret the entrainment patterns seen. Importantly, actigraphy can be implemented in everyday life, thus not altering behavior as a laboratory situation might do so, and is accepted by most psychiatric patients, even the most difficult.

CAVEATS IN ACTIGRAPHY

Outcome measures gathered with actigraphs (eg, sleep latency, IS, and IV) often are masked by everyday influences such as physical activity, meals, work schedules, and social demands. To add to the complexity, some of these environmental factors simply mask circadian rhythms without shifting them, but some of these factors (eg, environmental lighting conditions) will acutely affect and phase shift circadian rhythms. Thus, it is sometimes impossible to differentiate between a circadian disruption caused by malfunction of the biological clock or by environmental factors, or both. The circadian clock of a shift worker may work perfectly well, although his or her rest–activity cycle shows severe disruption as indexed by measures like the IS and IV.

To increase the quality in interpreting actigraphy measures, it is recommended to collect as much information as possible about the patient's daily routine by means of diaries. Furthermore, if feasible, one should add a circadian marker such as dim light melatonin onset (determined with the aid of a salivary melatonin diagnostic kit, for example SleepCheck Bühlmann Laboratories, Allschwil, Switzerland) to better discriminate between masking and circadian effects.

Fig. 1 shows rest–activity cycles of a working and nonworking partner in a healthy couple. The differences are particularly seen in the morning wake-up time and the contrast between workdays and weekends. This is an important point for comparing different clinical diagnoses, because the control subjects must live under similar conditions of employment to elucidate whether the differences found are related to the illness and not the sociological circumstances.

Thus, to avoid pitfalls with actigraphy, information of the patient's daily routine (diaries) should be gathered, a circadian marker measured, and if feasible, to compare patient groups only when they live under similar conditions of employment or ward schedules.

PHARMACOLOGIC TREATMENTS, DRUG ABUSE, AND CIRCADIAN REST–ACTIVITY CYCLES

There is mounting evidence that successful pharmacologic treatment in patients suffering psychiatric disorders also improves circadian entrainment, which is important for therapeutic efficacy. The mood stabilizers lithium and sodium-valproate used in bipolar patients have repeatedly been shown to alter circadian period, leading to a long period in humans.[11,12] The antidepressant fluoxetine also affects circadian output by producing a phase advance in the firing of neurons in the SCN.[13] Thus, antidepressants in the selective serotonin reuptake inhibitor class also may exert some of their effects on depression through modulation of the circadian clock. In contrast, circadian rhythm sleep disorders have been reported as a possible adverse effect of fluvoxamine but not fluoxetine.[14] The list of pharmacologic agents with repercussions on circadian clock function certainly will grow in the future.

A pharmacologic example suggests that a patient's response to different neuroleptic medications can impact significantly on the rest–activity pattern (**Fig. 2**). This patient suffering from Alzheimer's disease was prescribed haloperidol for behavioral disturbances after having a reasonably intact rest–activity cycle on risperidone. The disrupted circadian rest–activity cycle suggests an iatrogenic effect related to the drug rather than an effect of the illness per se,[15] because similar negative effects have been found in schizophrenic patients,[16] and even in a neurologic case with Gilles de la Tourette syndrome.[17] More important, the integrity of the circadian rest–activity cycle was related to cognitive function. This patient showed complete arrhythmicity developing with haloperidol concomitant with cognitive decline, that was reversed with clozapine, when cognitive improvement occurred.[15]

Another aspect of how drugs can alter circadian rest–activity cycles comes from patients who have addictive disorders. Even though it is known that these patients develop extreme sleep disturbances during drug withdrawal, there is no literature on possible disturbances of the circadian
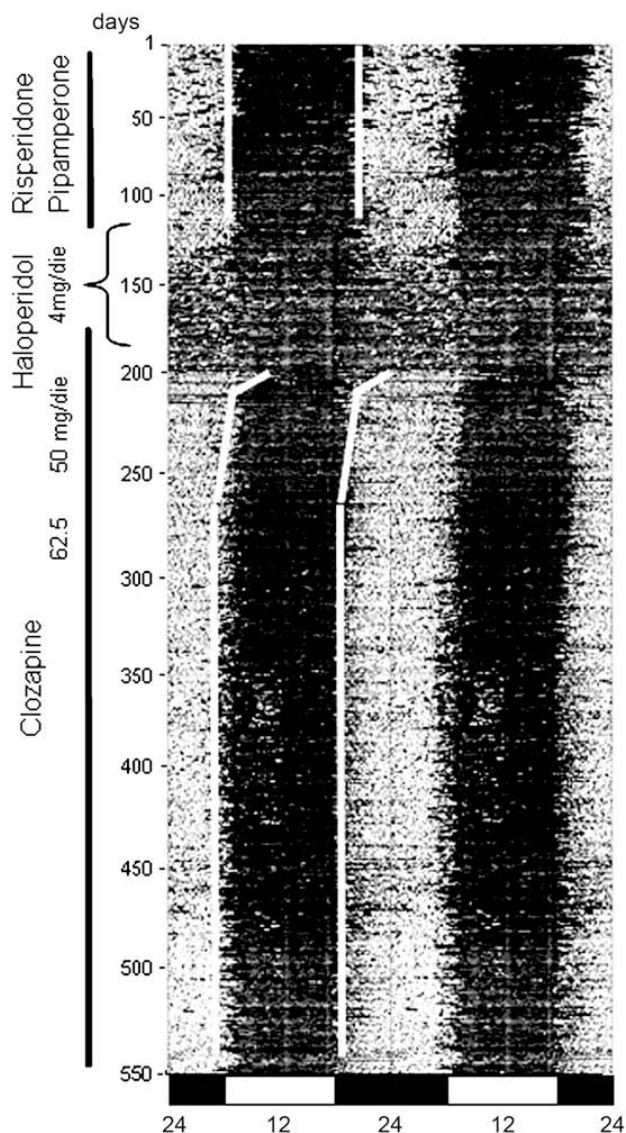
Fig. 2. Patterns of the circadian rest–activity cycle in a long-term recording over 550 days in a patient (54-year-old woman) with early onset Alzheimer's disease change with medications (double plot). The rhythms were entrained when the patient was on risperidone and clozapine. Changing to haloperidol treatment induced apparent total arrhythmicity. Note the rhythm re-emerging with clozapine treatment as a brief free run, and phase advancing with increasing dose (*From* Wirz-Justice A, Savaskan E, Knoblauch V, et al. Haloperidol disrupts, clozapine reinstates the circadian rest–activity cycle in a patient with early onset Alzheimer's disease. Alzheimer Dis Assoc Disord 2000;14:213; with permission.)

rest–activity cycle in drug dependence. An overlap of many psychiatric disorders with anxiety and addictive behavior has been noted.[18] Interestingly, an association between alterations in the human clock gene Per2 and increased alcohol intake in people was identified recently.[19] Given this evidence linking clock genes to reward behavior, a reappraisal of how sleep medicine could apply chronobiological principles to help these patients is warranted.

Again, in a single case study, an opiate-dependent patient whose rehabilitation and stabilization on methadone were successful, the persistent sleep disturbances and irregular sleep and wake times suggest that optimum stability had not been attained (**Fig. 3**). This is certainly an area requiring further study.

PATTERNS OF REST–ACTIVITY CYCLES IN INDIVIDUALS SUFFERING FROM DIFFERENT PSYCHIATRIC DISORDERS

Circadian rhythms are disrupted consistently in a spectrum of psychiatric disorders. In many cases, these disruptions may not be related directly to the circadian clock but to neural circuitries regulating output rhythms, or they may arise from conflicts between the internal biological clocks and environmental and social zeitgebers. Nevertheless, it has been difficult to establish whether circadian system disturbances can contribute to psychiatric disorders or whether they are merely symptomatic of the disease process. Disruption of circadian oscillators, however, clearly modifies disease severity, and in some instances, may play a more primary role in the etiology of the disease. More and more investigations of sleep timing in different psychiatric populations reveal a high incidence of comorbidity. For example, there is good evidence for comorbid delayed sleep phase syndrome in both childhood[20] and adult attention-deficit disorder,[21] and in obsessive–compulsive disorder.[22]

The following section shows individual actigraphs of patients suffering from different psychiatric illnesses to familiarize the reader with interpreting patterns of rest–activity cycles observed in daily routine psychiatry.

Bipolar Manic-Depressive Illness

Most studies looking at circadian rhythm disturbances in psychiatry have focused on depression, because of the clinical phenomenology (ie, diurnal variation of mood, early morning awakening, periodicity of the illness).[1,3] Most evidence for abnormalities in rhythms is available for bipolar manic-depressive patients. Cross-sectional studies reveal a preponderance of evening chronotypes, particularly during the depressed phase.[23,24]

The long-term actigraphy recording of an untreated bipolar patient (**Fig. 4**) illustrates circadian patterns already recognized and analyzed in the very early studies of actigraphy at the National Institute of Mental Health.[25–27] During the manic phase, sleep is short, fragmented, wake-up time extremely phase advanced, and nights
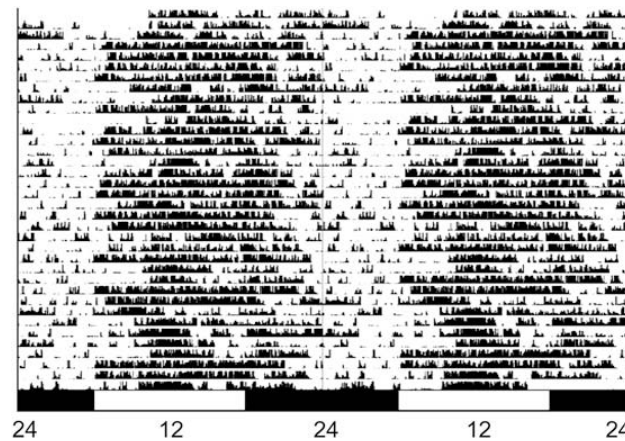
Fig. 3. Double plot of the circadian rest–activity cycle in a socially integrated methadone-substituted patient (28-year-old woman). (*Data from* A. Wirz-Justice, unpublished data, 2009.)

often characterized by spontaneous total or partial sleep deprivation.[27] This circadian rest–activity cycle resembles the extremely disturbed patterns seen in a mouse model of mania, the clock mutant mouse.[4] In contrast, as the patient switches into depression, the sleep phase lengthens, becomes more consolidated, and gradually phase delays. These dramatic alterations in sleep–wake behavior have been noted by the patient for more than 25 years and have occurred every 9 or 10 months independent of season. The patient never has been treated either pharmacologically or behaviorally for her illness. Although during her manic phase she was very compliant and motivated to collect saliva samples for melatonin assessments, during the depressed phase, she refused to collaborate, and it was difficult to convince her to continue wearing the actigraph. Thus, the question cannot be answered as to whether the marked change in her rest–activity cycles was caused by changes in the circadian clock (eg, shortened circadian period during manic phases as opposed to depressed phases). Interestingly, the increase in sleep length preceded the patient's recognition of having depression and lack of motivation by about 2 to 3 weeks.

Actigraphy studies in bipolar patients support the previously observed marked state-related shift in the circadian rest–activity cycle, a phase advance in mania,[28] and a phase advance after successful treatment for depression.[29]

Schizophrenia

Schizophrenia is perhaps the most devastating neuropsychiatric illness. Worldwide, the prevalence rate is approximately 1%. Although the etiology remains unknown, schizophrenia involves the interplay of susceptibility genes and environmental factors. Over 90 years ago, however, Bleuler pointed out: "in schizophrenia, sleep is

habitually disturbed." In times of severe psychotic agitation, schizophrenic patients may experience a profound insomnia or total sleeplessness. Severe insomnia is one of the prodromal symptoms associated with psychotic relapse. Patients also may develop sleep–wake reversals with a preference for sleeping during the day. Thus, the tendency toward a late sleep phase could be psychological (avoidance of interpersonal contact) or related to light-oriented behavior. In a series of careful studies, including measurement of melatonin rhythms at weekly intervals, Wulff and colleagues have shown that the timing of light exposure is reflected in the timing of sleep-wake
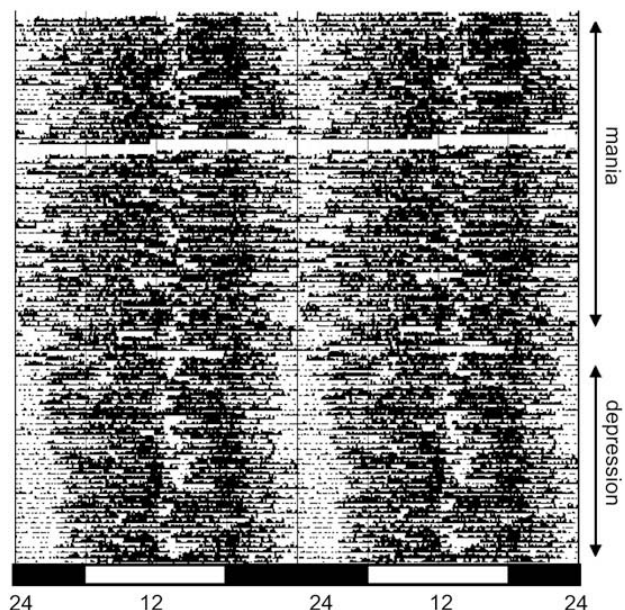

Fig. 4. Double plot of the circadian rest–activity cycle over many months in a bipolar patient (55-year-old woman). Clear changes in duration and timing of rest are seen in the shift from mania (*above*) to the depressive phase (*below*). (*Data from* C. Cajochen, unpublished data, 2009.)
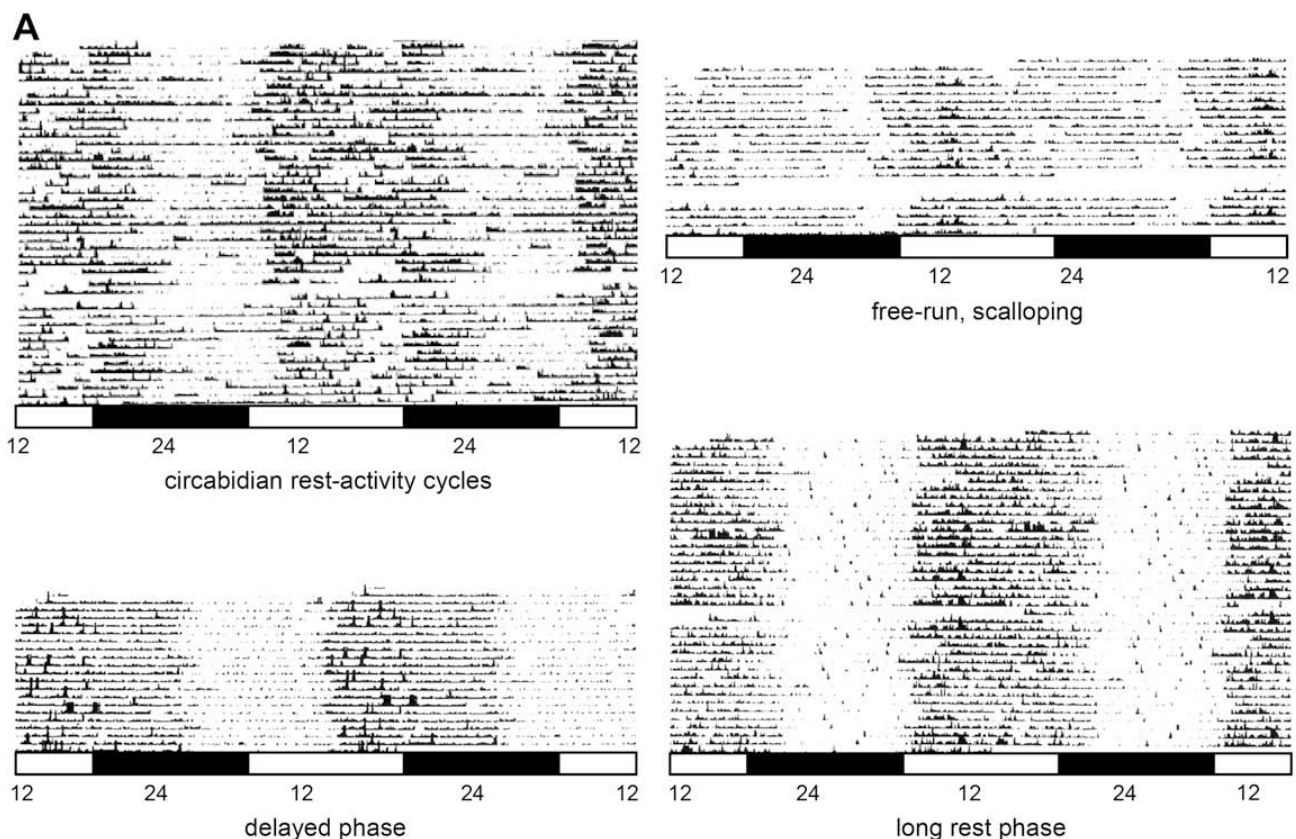
Fig. 5. Double plot of the circadian rest–activity cycle in seven patients diagnosed with schizophrenia. All patients were hospitalized and treated with monotherapy. (*A*) The four panels represent patients treated with the classical neuroleptics haloperidol or fluphenazine. (*B*) The three panels represent patients treated with the atypical neuro-leptic clozapine. Occasional missing data are left blank. (*From* Wirz-Justice A, Haug HJ, Cajochen C. Disturbed circadian rest–activity cycles in schizophrenia patients: an effect of drugs? Schizophr Bull 2001;27: 499; with permission.)

cycles.[30] By getting up late, the patients lack morning light exposure to establish a phase advance, and drift to later. The most striking example was a single patient whose rest–activity cycle and melatonin rhythms free ran in winter (when, presumably, the opportunity to have suffi-cient light was reduced) but did entrain during summer (K. Wulff, personal communication, 2009). By measuring rest–activity rhythms in unemployed but otherwise healthy controls, they were able to show that patients with schizophrenia are not phase delayed only because of lack of social zeitgebers.[31] Thus, light-oriented behavior may be one important factor in these sleep–wake cycle abnormalities.

Nurses and physicians clearly recognize that some of their schizophrenic patients exhibit abnormal sleep–wake cycles. The first long-term (longer than 1 year) wrist activity recording in one schizophrenic patient revealed virtually continuous activity without prolonged bouts of rest and no day–night differences.[32] Despite this abnormal sleep–wake behavior, the patient's circadian profile of melatonin secretion showed a clear 24-hour rhythm, indicating that his circadian clock

functioned properly. Also, when the patient was studied in the chronobiology laboratory under a 31-hour bed rest protocol with free choice of sleep times, core body temperature exhibited a circadian modulation, albeit with very small amplitude, but his sleep–wake propensity rhythm showed a clear reversal (wake at night, sleep during the day). In the same patient, the authors documented that a change from haloperidol to clozapine treatment improved rhythmicity.[32] In a follow-up study, rest–activity cycles were re-corded in a larger patient cohort.[16] Many patients who had schizophrenia (whether hospitalized or under home conditions) showed unusual rest–activity cycles. Furthermore, a given patient's response to neuroleptic medications impacted significantly on their rest–activity patterns. The circadian rest–activity cycle of patients stabilized for more than a year on monotherapy with a clas-sical neuroleptic (haloperidol, flupenthixol) or with the atypical neuroleptic clozapine was docu-mented by continuous activity monitoring for 3 to 7 weeks. The three patients treated with clozapine had remarkably highly ordered rest–activity cycles (**Fig. 5**B), whereas the four patients on classical
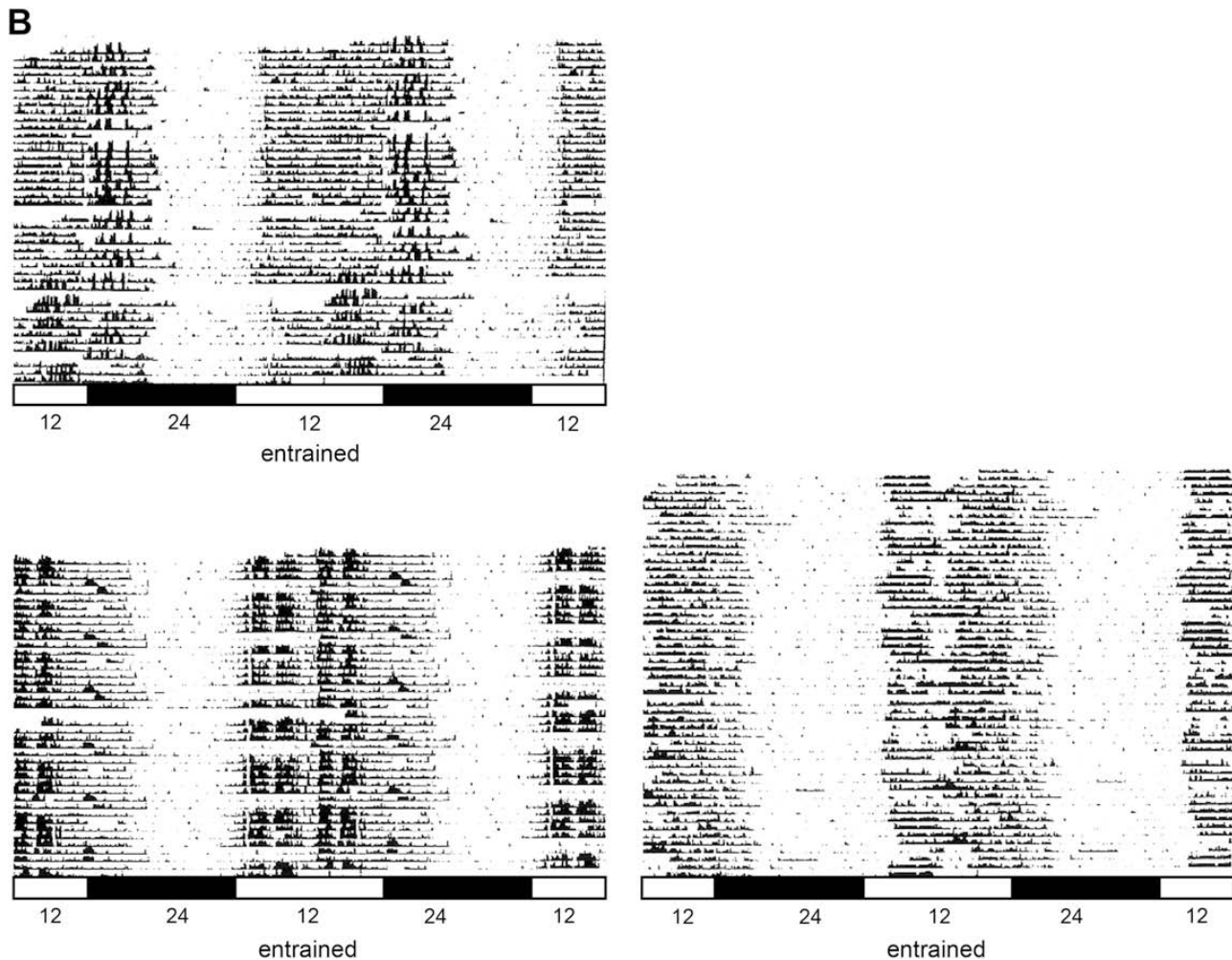
B

Fig. 5. (*continued*)

neuroleptics had minor to major circadian rhythm abnormalities (see **Fig. 5**A).[16] This observation could be conceptualized in terms of the two-process model of sleep regulation. High-dose haloperidol treatment may have lowered the circadian alertness threshold, initiating polyphasic sleep episodes, whereas clozapine increased circadian amplitude (perhaps through its high affinity to dopamine D_4 and serotonin $5HT_7$ receptors in the SCN), thereby improving entrainment.

What are the chronobiological disturbances in schizophrenia? The etiology is probably neither primarily an abnormality of the homeostatic process (although reduced slow-wave sleep or EEG slow-wave activity has been documented) nor an abnormality of the circadian process (although medicated patients in free run show a shorter endogenous periodicity).[2] The combination of diminished social zeitgebers, late sleeping, and light exposure in the evening rather than morning all interacting with medication effects leads to altered internal and external phase relationships. In turn, these altered sleep patterns may reinforce the difficulties with cognitive function and social engagement, and the depressive symptoms associated with schizophrenia.

Ongoing actimetry studies reveal that the higher the relative amplitude of the rest–activity cycle, the better the cognitive function in this patient group.[33] These preliminary data (**Fig. 6**) suggest that efforts to enhance robustness of entrainment may provide a means of improving behavior, that, in turn, allows better rehabilitation, even though not directly treating the underlying illness.

Broadly viewed, these studies provide consistent evidence of circadian dysregulation in schizophrenic patients. Although commonly present, however, it is not clear whether the observed circadian alterations are just an epiphenomenon of the disease (or its treatment) or causally involved, or both.

Borderline Personality Disorder

Many research groups studying delayed sleep phase syndrome have noted the prevalence of accompanying personality disorders, but without finding a reliable strong relationship. The converse
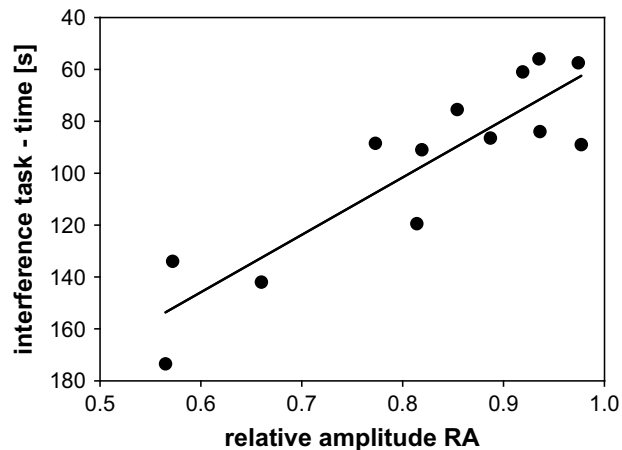
Fig. 6. The Stroop color word interference task is a measure of executive function/reaction inhibition. Reaction time in the Stroop test is faster in patients with schizophrenia whose circadian rest–activity cycles are more stable, as measured by the relative amplitude of the rhythm (N = 13; r = 0.758, P = .003). (*Data from* V. Bromundt, unpublished data, 2009.)

also may be true; in an ongoing study of circadian rest–activity cycles in borderline personality disorder, delayed sleep phase syndrome was rather prominent. Closer investigation, however, revealed a variety of patterns, ranging from relatively normal to extremely disturbed (**Fig. 7**).

Preliminary findings suggest that the use of light therapy has positive effects not only on (actigraphy-defined) sleep characteristics but also on aspects of the borderline symptoms themselves (V. Bromundt and colleagues, unpublished data, 2009).

Alzheimer's Disease

There is a large body of evidence demonstrating a reduction of SCN function with aging that is exacerbated in Alzheimer's disease (AD), and

many studies have used zeitgebers to stimulate and thus better entrain the remaining SCN neurones (see the article by Zee and Vitiello in this issue), notably the recent long-term trial of light with or without concomitant melatonin treatment showing stabilization of cognitive function, mood, and the rest–activity cycle.[34]

At a late stage of life, however, it is not only diminished SCN function that determines the altered sleep-wake cycle in Alzheimer's patients, or specific medication (as in **Fig. 2**). A combination of multimorbidity, combined medications, isolated life style with few social zeitgebers, and little outdoor light exposure can interact to produce the kind of rest–activity cycle seen in **Fig. 8**. Circadian studies of major disease entities are in their infancy, and the complexities of comorbidity and poly-medication have not been addressed.

Korsakoff's Psychosis

Not every dementia is a circadian disturbance. The dramatic disruptions in the rest–activity cycle of patients who have AD (see the article by Zee and Vitiello in this issue) are not the same as in patients who have vascular dementia.[7] In patients who have Korsakoff's psychosis, no evidence of abnormal circadian rhythm phase is apparent; the rest-activity cycle is extremely well-entrained, more so, even, than the matched control subjects (**Fig. 9**). What is characteristic, however, is a marked amplitude diminution—low daytime activity and a long rest phase.[35]

ZEITGEBERS AS THERAPY

The previous examples and indications point toward the use of chronobiological therapies in many of the sleep disorders associated with psychiatric illness. Chronotherapeutics—treatments based on the principles of circadian rhythm

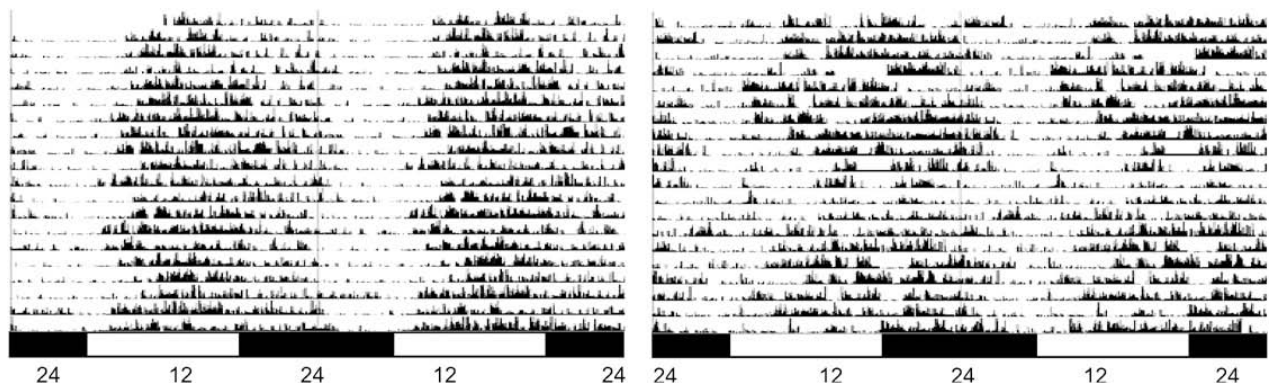**Fig. 7.** Double plot of the circadian rest–activity cycle in two patients with borderline personality disorder, ranging from relatively well entrained (*left*) to extremely disrupted (*right*). (*Data from* V. Bromundt, unpublished data, 2009.)

Fig. 8. Single plot of the circadian rest–activity cycle in a patient with probable Alzheimer's Disease (79-year-old woman). Grey background = light exposure. Which of the other illnesses in addition to Alzheimer's disease in this patient (coronary heart disease, occlusive arterial disease, kyphoskoliosis with lumbago, glaucoma) could have contributed to the clearly disturbed sleep? Furthermore, which of the patient's medications (haloperidol, trimipramine, oxazepam, omeprazole, aspirin) and/or their interaction with previously mentioned illnesses impacted the most on the circadian rest–activity cycles? Her main zeitgeber was the 1-hour visit of her son faithfully every evening around 7 PM (*Data from* A. Wirz-Justice, unpublished data, 2009.)

organization and sleep physiology—offer mental health practitioners a set of nonpharmacological, rapid, and effective antidepressant modalities for monotherapy or as adjuvants to conventional medication, particularly in major depression.[36]

Light Therapy

Light therapy can be considered the most successful clinical application of circadian rhythm concepts. The most obvious application in sleep medicine has been to phase shift and re-entrain sleep–wake cycle disorders, whether delayed or advanced sleep phase syndrome, or age-related alterations.[37] Light is the treatment of choice for winter depression.[38,39] There is already good evidence for efficacy in bulimia and preliminary evidence for usefulness in pre- and post-partum depression, both clinical indications where

nonpharmaceutical therapies are needed.[40] Particularly promising are the antidepressant effects when used as an adjuvant in nonseasonal major depression.[41,42] Improving the irregular rest–activity cycles often found in patients who have AD[34,43] and demented elderly in general represents another important application of light therapy.[44,45] Light is being recognized not only as a major zeitgeber necessary for daily well-being (with applications in the work place and in architecture) but also as a "drug" that can be prescribed in dose, timing, duration, and spectral composition for specific diagnoses.[41,42]

Dark Therapy

Single case studies of rapidly cycling bipolar patients have shown that extending darkness (or rest, or sleep) immediately stops the recurring pattern, a rather astonishing result in these therapy-resistant patients.[46,47] Further support for the relevance of these findings is that extended darkness (not rest, and not sleep) in manic bipolar patients can control their symptoms within days.[48] A novel approach, which is perhaps easier than shutting up manic patients in dark rooms, is the use of blue-blocking sunglasses.[49] The recent discovery of a blue wavelength-sensitive photopigment in retinal ganglion cells, melanopsin, responsible for the major nonvisual photic input to the SCN, suggests that some of the circadian effects of light can be prevented by filtering out the blue wavelengths.

Melatonin

In circadian physiology, melatonin is important for timing the cascade of events initiating sleep. The nocturnal onset of melatonin secretion opens the gate for sleep propensity, which involves peripheral thermoregulatory mechanisms.[50,51] The warm feet effect of melatonin underlies its soporific action and usefulness in various sleep disorders.[51,52] The few studies administering melatonin to depressed patients have found improvements in sleep, but not in mood.[53,54] Melatonin is a zeitgeber and can enhance entrainment (see the examples of its sleep–entraining properties in blind persons in the article by Uchiyama and Lockley in this issue). Given the development of low-dose and controlled-release formulations, there is an important future for melatonin as a useful long-term sleep/rhythm promoting agent with fewer adverse effects than the hypnotics, and in addition, for the newer melatonin agonists (see the article by Rajaratnam, Cohen, and Rogers elsewhere in this issue).
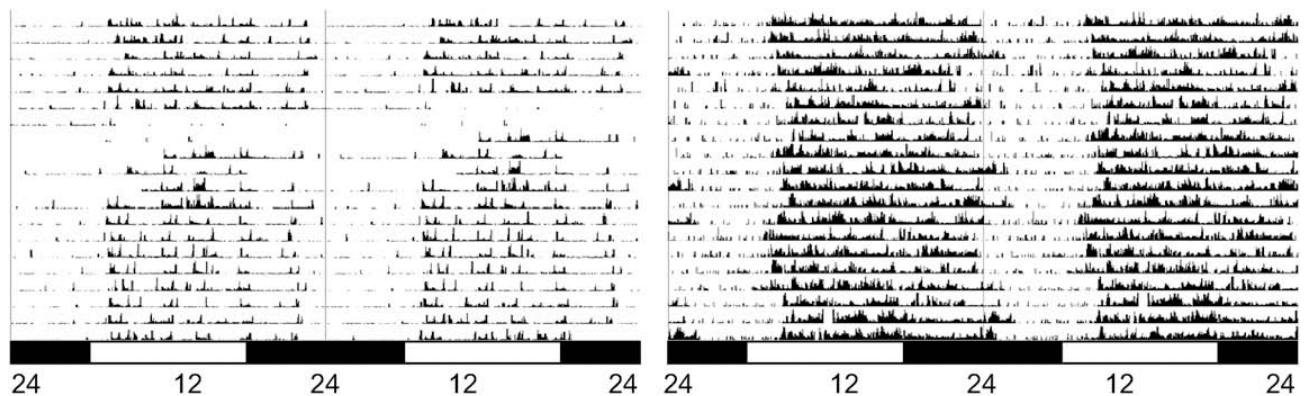
Fig. 9. Double plot of the circadian rest–activity cycle in a patient with Korsakoff's psychosis (61-year-old man, *left*) and an age-matched community-living control subject (*right*). (*Data from* A. Wirz-Justice, unpublished data, 2009.)

CIRCADIAN RHYTHMS AND PSYCHIATRY: WHAT IS IMPORTANT?

The different individual examples hopefully have provided a purview of the enormous variety of sleep–wake cycle disturbances in psychiatric patients. This indicates an important role for actigraphy in defining the circadian rest–activity cycle pattern in many psychiatric disorders. The quality of entrainment may provide information that cannot be obtained otherwise about sleep timing and organization; it also may prove to be an outcome measure of successful treatment. The strategy of attending to entrainment of patients is a restatement, with better understanding of putative mechanisms, of establishing daytime activities as part of the therapeutic strategy. In fact, development of interpersonal and social rhythm therapy for improving occupational functioning in bipolar patients has focused on this aspect.[55]

The rules for good entrainment are adapted from those generally in use in sleep medicine (**Box 1**).[8]

Box 1
Circadian rhythms and psychiatry—what is important?

Stable external and internal phase relationships:

Appropriate entrainment of the sleep–wake cycle to the external light–dark cycle

Enough light during the day, enough darkness during the night

Adequate retinal function

Sufficient social zeitgebers

Reconsider the zeitgeber function of timed activity and meals

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SUMMARY

Although actigraphy is being used more often now in sleep medicine, its use in psychiatry remains rare. Examples from daily clinical practice illustrate that circadian sleep–wake cycle disturbances are widespread in psychiatric illness. The problems of entrainment that are revealed by actigraphy—irregular, arrhythmic, phase delayed, advanced, or even free-running rest–activity cycles—can arise from different causes. The usefulness of these measurements is not only to better understand underlying etiology but to point the way to treatment possibilities. Many physicians increasingly are using light therapy to treat depression; melatonin is being used for delayed sleep phase or free-running rhythms. Although these treatments are effective for many individuals, they still have limitations. We can generalize, however, that all techniques promoting entrainment can be used as pragmatic adjuvants to the illness-specific medication and psychotherapies. An understanding of how these techniques alleviate psychiatric symptoms and how proper entrainment may result in changes in mood and cognitive behavior will allow the design of less-invasive and more effective treatment modalities for these devastating psychiatric illnesses.

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