Biological rhythms and mood disorders

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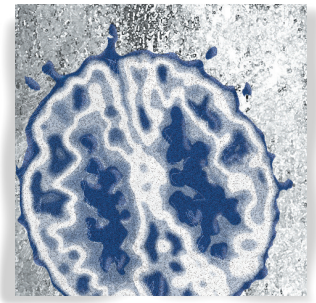

Integration of several approaches concerning time and temporality can enhance the pathophysiological study of major mood disorders of unknown etiology. We propose that these conditions might be interpreted as disturbances of temporal profile of biological rhythms, as well as alterations of time-consciousness. Useful approaches to study time and temporality include philological suggestions, phenomenological and psychopathological conceptualizations, clinical descriptions, and research on circadian and ultradian rhythms, as well as nonlinear dynamics approaches to their analysis.

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Introduction

Of the seasons of the year,
the autumn is most melancholy…
(Burton, 1621)[1]

As a science matures, it pays more attention to the temporal dynamics of its target phenomena. The relatively young discipline of psychiatry shows exactly this trajectory, with the temporal dimension receiving growing research interest. This development is quite obvious in the domain of mood disorders, where time features in the diagnostic description, phenomenology, and increasingly our causal understanding of the disorders. It is therefore timely to provide an overview of this expanding area. The aims of this article are fourfold. First, we introduce some *philological considerations* about the relationship between time and mood. Secondly, we review the (largely European) *clinical literature* which has focused on the sense of time in mood disorder phenomenology. Thirdly, we provide a synopsis of the range of *empirical evidence* indicating that biological timing (particularly circadian rhythms and sleep/wake processes) is critical in the etiology of mood disorders. Finally, we present nonlinear dynamical approaches applied to the analysis of the measures related to psychological time series. The intent of the article is to encourage an open, multidisciplinary approach to generate testable hypotheses about temporality in the mood disorders.

Contributions of philology and natural philosophy

As often happens in the evolution of theoretical concepts relevant to psychopathology, early intuitions and illuminating insights can often be found in ancient mythology, philosophy, and art.[2] Since ancient times in Western culture, melancholia and mania have been related to characterological and temperamental constellations of the Greek god, Kronos, and of his Latin counterpart, Saturn. Later, the implacable influence of the planet Saturn was often invoked as a symbolic representation of older religious archetypes, even as naturalistic approaches to the study of mood disorders emerged during the Renaissance.[3]

The Kronos-Saturn hybrid can be summed up as a quintessential ambivalent coexistence of contradictory forces of light and darkness, life and death, rationality and folly, of the highest and most sublime spiritual contemplations and most miserable and lowest confinements of the world, or even the netherworld. The concept was conceived of as the "absolute master of time," the mighty principle of cosmologic unity, the "One that devours and consumes everything." Indeed, the ancient Greek name literally means "time" and the Latin term is translated as "filled or satiated by years." Moreover, iconographic representations portray Kronos-Saturn devouring his own children (except Zeus), concretely conveying the idea that time indeed makes events precipitate into an abyss and disappear into oblivion.[3] Meaningful correlations between melancholic states and the dimension of time and temporal flow has become an important frame of reference for psychological and biological studies of affectivity and mood.

Contributions of phenomenology and classical psychopathology

Von Gebsattel,[4] Strauss,[5] Minkowski,[6] and Tellenbach[7] have highlighted the important role of temporality in phenomenological psychopathology. Drawing on philosophical concepts of Bergson, Husserl, and Heidegger, these authors have analyzed deviations or distortions of time-experience, mainly from an individual subjective perspective. They and others have noted a slowing down or inhibition of time-experience or, in strictly phenomenological terminology, of lived time in depression and an acceleration of perceived time-experience in mania.[8,9] Lived time includes a social dimension that allows for harmonizing subjective and interpersonal time-experience as a contribution to a sense of past, present, and future.

Subjective lived time and its reference to interpersonal time-experience are bound together in the dimensions of past, present, and future. Indeed, the dynamics of everyday interactions imply habitual synchronization. They bring about a fundamental feeling of being attuned to the time of others, and living with them in the same "inter-subjective temporality."[8] Lived time is primarily a lived synchronicity with the environment and with others. It is only from periodic desynchronizations, commonly associated with loss, guilt, or separation, that the experience of "not-yet" or "no-more" results.

According to Fuchs,[8] it is not that synchronization brings about the awareness of lived time; on the contrary, this occurs from disturbances caused by biological or psychosocial factors. The processes of subjective time and interpersonal time normally unfold more or less together and influence each other. This exchange results in a sense of being in "lived synchronization" with others and of being "in tune" with the time of others.[6] For example, during "melancholic episodes," some individuals may become disengaged from interpersonal time and live in their own subjective inner temporality. In some temporally distorted experiences of severe melancholia, there is no future and the past is fixed. During these melancholic episodes while external interpersonal time still flows and measured time still has duration and lapses or intervals, lived time is instead experienced as a slowing down or stopping of subjective inner time-experience because it is experienced or measured against interpersonal time.

Fuchs considers this a failure of attunement of affect with others, or inability to participate emotionally in other persons or things or to be affected by them.[8] Painfully, the melancholic experiences his/her rigidity in contrast to the movements of life going on in his/her environment. Kupke observes that some melancholic states involve suffering from a break between one's own, subjective time and an extraneous objective time, experienced as a falling behind, slowing down, or a total standstill of subjective temporality, with a desynchronization between inner and external time-experience that causes psychopathological distress.[10] Such desyn-

chronizations become apparent because human activity tends toward the future—a future that includes interpersonal time; in the suspension of activity or radical passivity, lived time is reversed because the future comes toward the inactive individual who simply waits for the future to become present, with a loss of normal future-orientation, of "being after something," or of "appetitive tension."[8]

Temporality is a field of shortage or a realm of void to be constantly fulfilled, which is ignored only insofar as one's needs are not met, because one is never satisfied by the next moment as each moment in turn generates the potentiality of the next, yet-to-come. This need is always "now," as the present is at least partially constituted by openness onto the future. This openness has direction and intentionality toward closure and fulfillment. One of Minkowski's depressed patients reported the following: "I feel the desire to act, but this produces an opposite reaction to that of normal people; the phenomenon of stopping surges up and causes a complete discouragement…and I have the sensation of a negative void."[6]

Patients with a severe depression may develop hypochondriacal delusions, Cotard's syndrome (belief of being dead), or other nihilistic beliefs, and they may describe a static structure of time in which there is no change, no beginning or end, with the horror of now, the eternal, ever-present, and never-changing.[11] The very process of undertaking a psychiatric assessment that requires eliciting a *history* is made problematic. Nietzsche's well known "thought experiment"[12] points to the same disturbance of temporality that might underlie both severe depression and psychotic mania:

> What if some day or night a demon were to steal after you into your loneliest loneliness, and say to you: "This life which you live and have lived, must be lived again by you, and innumerable times more." And there will be nothing new in it, but every pain and every joy and every thought and every sigh—everything unspeakably small and great event in your life—must come again to you, and in the same sequence and series… The eternal hourglass will again and again be turned—and you with it, speck of dust! Would you not throw yourself down and curse the demon who spoke to you thus? Or have you once experienced a tremendous moment, in which you would answer him: "Thou art a god, and never have I heard anything more divine!"

If melancholic time-distortion in Cotard's syndrome is a symptom of severe depression, then the Superman syndrome (conviction of being almighty and without limits) may be the affective epiphenomenon of temporal distortion in the heights of grandiosity and mania. Eternal torment and eternal divinity may be two aspects of the same temporal phenomenon.

Phenomenological disturbances of sensed time, although not always seeming to be of great importance, usually indicate that something is going wrong. For example, melancholic depersonalization is accompanied by a serious disturbance of temporality, a sense of inhibition of "becoming." Even the most limited ability to separate events into past, present, and future; to estimate duration; and to place events in sequence appears to be necessary for intellectual processes to be carried out satisfactorily.[13] With a decline in worldly activity the sense of time is altered, resulting in protraction, slowing, and an impoverished "now" characterized as boredom. A "loss of vital contact" or a loss of "affect attunement" with the world may result in activity "drying up."[6,8,14] Certain pathological experiences so dramatically alter the temporal microstructure of experience that an individual's sense of subjective lived time is restructured and disordered. In these circumstances, temporality may, as a result of the overwhelming presence of suffering, involve a past, present, and future that are no longer moving apart. Normally, past and future withdraw on their own, in accordance with their nature of "not being." The future is characterized phenomenologically as openness to change and movement; without such openness, the future appears static and deterministic, and the result may well be hopelessness, despair, and seemingly eternal suffering.[14]

The habitual ways of human beings in the world imply, from early childhood, synchronization with the dialectic rhythms of life. These include such environmental "timings" as wake-sleep cycles, ultradian and circadian secretions of hormones, and other bodily activities. These biological rhythms are influenced by planetary, lunar, and solar temporal and seasonal rhythms; and, in terms of one's complex interpersonal life, by family living patterns, timetables, work schedules, and social protocols. In the next section we discuss the altered rhythmicity and abnormal temporality aspects of mood disorders from the perspective of clinical psychiatry and biological rhythm research.

Clinical studies and biological rhythm research

Clinical observations

Alterations in time sense may contribute causally to depression, or at least to its continuation. It is noteworthy that some effective treatments for depression involve seeking to trick a patient's "cognitive timer" or "internal clock." Observers of melancholia have linked many of its clinical symptoms to abnormal biological rhythms.[15-17] Diurnal variation of mood and early morning awakening in depression are incorporated into established diagnostic systems for mood disorders, as has the concept of seasonal variation of mood, usually with fall-winter depression.[18] Not only is sleep disturbed, but also many circadian rhythms measured in depressive patients are abnormal: earlier in timing, diminished in amplitude, or of greater variability.[19] Bipolar disorder (BPD) patients, and particularly those with rapidly fluctuating mood and behavior ("rapid-cyclers"), undergo remarkably precise periodic switches between clinical states.[20]

Moreover, when social arrangements alter the natural organization of biological rhythms beyond its limits of adaptability, as in protracted shift work or sustained jet-lag conditions, vulnerable individuals tend to manifest physical debilitation which has similarities to that of endogenomorphic depression, with weight loss, anergia, and irritability.[21] In addition, both light boxes and sleep deprivation are potent ways to elevate mood, and may even trigger a manic episode in a person with bipolar disorder. Whether these circadian rhythm disturbances are of etiological significance for mood disorders or a consequence of altered behavior is not clear.

The term circadian refers to a cycle of approximately one day that may run slightly longer or shorter than 24 hours. Evolution has endowed us with a biological system that is highly responsive to time-givers (*Zeitgebers*), stimuli in the environment that cue the system so that our circadian rhythms become synchronized with the activity in the world around us. Our system is particularly sensitive to the zeitgeber light. An active process known as entrainment keeps our system aligned with external time and allows it to shift as the balance of light and dark varies across the seasons, and as we travel from one time zone to another.[22]

The biological clock in the suprachiasmatic nuclei (SCN), a master pacemaker driving circadian rhythms in brain and body, is synchronized to the external light–dark cycle. Several studies have suggested that BPD is characterized by enhanced light sensitivity especially if administered in the morning versus midday.[23] Melatonin and cortisol are markers of the circadian clock that modulate the sleep-wake cycle. In one study bipolar patients exhibited lower melatonin levels and a later peak time for melatonin during the night relative to a healthy comparison group.[24] In another study bipolar manic patients showed higher cortisol levels during the night and an earlier nadir for plasma cortisol relative to healthy control subjects.[25] Lithium has shown to slow down circadian periodicity and can modify circadian cycle length across species.[26] Indeed, in a case series of seven rapid-cycling bipolar patients studied under naturalistic conditions throughout complete manic-depressive cycles, five exhibited a circadian rhythm that ran fast, and in these participants lithium slowed the rhythm.[27]

The social zeitgeber theory suggests that episodes of depression and mania or hypomania arise as a consequence of life events which disrupt social zeitgebers such as mealtimes and bedtimes, derailing by these timing changes the circadian rhythms and triggering relapse. Evidence for the various predictions of this theory is accruing and the treatment derived from it, interpersonal and social rhythm therapy, has been shown to be effective in reducing relapse in BPD.[28] A significant improvement in mood is observed in 40% to 60% of depressed BPD patients after total or partial sleep deprivation.[29]

Basic research findings

The internal coincidence model proposes that depressed patients sleep at the wrong biological clock time because the phase angle between the biological clock and the sleep-wake cycle is out of alignment.[30]

The two-process model instead proposes that sleep is modulated by the interaction of a homeostatic process of rising sleep pressure (Process S) dependent on the duration of prior wakefulness, that is dissipated during the sleep period, and a circadian pacemaker (Process C) that ticks along independent of sleep. It has been proposed that depression is characterized by a deficiency in the Process S that could manifest itself in a slower buildup of sleep pressure during wakefulness or a different rate of decline during sleep. Therefore, a full night's sleep deprivation may cause a short-term

increase in Process S to normal levels. A deficit in Process C could be manifested in changed amplitude, phase, or endogenous period. Shifting phase relationships between C and S can cause, in vulnerable individuals, decrements in mood.[19]

At the neural systems level, circuits involved in affect regulation and circuits involved in sleep regulation are known to interact in bidirectional ways.[31] In a study comparing healthy subjects who were sleep-deprived with healthy subjects with normal sleep, the ones undergoing sleep deprivation showed more than 60% greater amygdala activity. This large increase was associated with a loss of activity in the medial-prefrontal cortex which exerts top-down control on the limbic areas (including the amygdala) and functions to modulate emotional responses so they are appropriate to the context. Sleep may contribute to maintaining the connectivity between the medial-prefrontal cortex and the amygdala, which is critical for responding appropriately to emotional challenges the next day.[32]

Genetic vulnerability to BPD can therefore involve a bidirectional relationship between daytime affect regulation and nighttime sleep, such that an escalating vicious circle of disturbance in affect regulation during the day interferes with nocturnal sleep/circadian functioning, and the effects of sleep deprivation contribute to disruption of affect regulation the following day.[22]

Individuals have different preferences for timing their sleep.[33] This chronotype ("larks" or "owls") is partially determined by clock genes. Also, genetic sleep disorders such as familial advanced phase sleep syndrome (FASPS) in which individuals have shifted circadian rhythms and fall asleep and wake up much earlier than desired, or delayed sleep phase syndrome (DSPS) which has the opposite phenotype, manifest allelic mutations on one or other of the clock genes[34-36] and are both highly comorbid with depression and anxiety.[37] In addition, BPD patients are more likely to exhibit an evening than a morning chronotype.[38]

Circadian rhythm disturbances in BPD have led to a search for genetic abnormalities in circadian ''clock genes'' potentially associated with the illness. Nevertheless, no significant clock gene findings have emerged from genome-wide association studies (GWAS) so far, probably due to several issues including: (i) the disease vulnerability complexity, most likely involving a polygenic substratum; (ii) the more complex organization of the biological clock than previously recognized; and/or (iii) genetic risk for BPD that may be shared across multiple illnesses.

To investigate these issues, McCarthy and colleagues considered the clock gene network at three levels: essential "core" clock genes, upstream circadian clock modulators that influence the period and/or the amplitude of rhythms by altering protein stability, cellular distribution, or phosphorylation of proteins within the core clock, and downstream clock-controlled genes.[38] Using relaxed thresholds for GWAS statistical significance, they determined the rates of clock versus control genetic associations with BPD, and three additional illnesses that share clinical features and/or genetic risk with BPD (major depression, schizophrenia, attention deficit/hyperactivity).

The authors also compared the results with a set of lithium-responsive genes. Associations with BPD-spectrum illnesses and lithium responsiveness were both enriched, ie, at a rate higher than would be expected by chance, among core clock genes but not among upstream clock modulators. Associations with BPD-spectrum illnesses and lithium-responsiveness were also enriched among pervasively rhythmic clock-controlled genes but not among genes that were less pervasively rhythmic or nonrhythmic. These findings suggest that previously noted associations between circadian rhythms and mood disorders may not be likely explained by a common process upstream of both the circadian clock and mood regulatory mechanisms, but rather argue for a more fundamental connection between the clock and the mood.

Circadian clock-related polymorphisms may be related to susceptibility to seasonal affective disorder (SAD) together with evening chronotype.[39] Taken together the results indicate that it is unlikely that affective disorders will be characterized as simple clock gene mutations.

Individual genetic characteristics of the molecular mechanisms of the biological clock are also determinants of core features of mood disorders, including age at onset,[40] recurrence,[41] symptoms of insomnia and its treatment,[42,43] and response to sleep deprivation.[40] Such findings point to an intimate relationship between the neurotransmitter systems targeted by drugs and the circadian rhythms targeted by chronotherapeutics. Because the timing of sleep appears relevant for determining mood state, genetic factors may provide a chronobiological vulnerability for depression and affect dysregulation, in that wrong or poor alignment of internal phase with the side

world increases susceptibility to depressive as well as dysphoric mood swings.

New findings on desynchronization in clock gene expression may illustrate the chronobiological vulnerability for depression and affect dysregulation. The clock genes in the SCN gradually adapt to a phase shift of the light–dark cycle (as found in shift work, transmeridian flight), whereas clock genes in the muscle, liver, and lung resynchronize at their own rates.[44] This results in a "double desynchronization"—"internal desynchronization" between different clocks in the body and brain, and "external desynchronization" between the timing of body rhythms with respect to the light–dark cycle. As Wirz-Justice has pointed out in a review paper, the temporal orchestra can get quickly out of tune and this misalignment has profound effects on mood, sleep, and health.[19] Genetic vulnerabilty and stress influence circadian rhythms and sleep patterns, leading to symptoms characteristic of affective disorders.[45] Specifically, genetic vulnerability may influence circadian rhythms and sleep patterns by a decreased cellular resilience associated with lower resistance to stressful events, thus leading to affective disturbances.[45-48]

Circadian regulation interacts with, and is determined by, neurotransmitter function; for example, the highest concentrations of central nervous system (CNS) serotonin are in the SCN.[49] CNS serotonin turnover undergoes marked circadian and seasonal rhythmicity[50] and is rapidly stimulated by light exposure.[51] This links the important role of light as zeitgeber or synchronizer of the circadian system, to the role of serotonin in mood disorders, indirectly supported by combination therapies of light and selective serotonin reuptake inhibitors (SSRIs).[52,53]

Stable internal and external phase relationships appear to be crucial for a stable and euthymic mood state. Any misalignment brings with it the propensity for mood fluctuation, particularly in vulnerable individuals. Chronobiological concepts emphasize the important role of zeitgebers to stabilize phase, with light and melatonin being the most important. But other zeitgebers, such as dark (and rest) periods, regularity of social schedules and meal times also play a role. Regular dark phases themselves appear to regulate the mood swings of rapid cyclers,[54] and, in a preliminary trial, "dark therapy" diminished manic symptoms as rapidly as the conventional antipsychotics generally used.[55]

Psychomotor activity and sleep-wake cycle disturbances are core symptoms of mood disorders, often heralding later emerging affective changes. Different locomotor activity as well as sleep patterns appear to be specific to particular types of affective illness, for instance observed psychomotor activity changes in anergic-hypersomniac bipolar depression versus agitated-insomniac unipolar depression.[56] Studies on the objective assessment of these features in relation to circadian rhythms have contributed to the understanding of the pathophysiology of affective illnesses. In the next section we discuss the psychomotor activity studies in affective disorder patients.

Actigraphy studies

Psychomotor activity and its temporal rhythms provide valuable quantitative and objective assessments of psychiatric patients, particularly with affective or attentional disorders.[57,58] Such activity is conveniently recorded with wrist-worn piezoelectric actigraphic devices with microprocessors that provide objective, quantitative evaluation of motility levels and their dynamic changes over several days. Actigraphy also distinguishes sleep from waking, and can indicate specific sleep phases.[57,59-62]

Analyses of activity data document a substantial phase-advance (*earlier* daily peak [*acrophase*]) of circadian activity cycles in bipolar disorder (BPD) patients,[63,64] in contrast to a more likely phase-delay (later acrophase) in unipolar major depressive disorder (MDD),[65] seasonal affective disorder (SAD),[66] and winter depression in BPD with seasonal pattern.[57]

Circadian activity phase-delay, estimated crudely with daily sleep logs and self-reports of morning versus evening activity levels, was associated with low winter mood in the general population and SAD patients.[67-69]

Circadian phase variation was addressed indirectly by evaluating a measure based on individual preference for activities in the morning versus evening in BPD patients, who differed significantly from controls and schizophrenia or schizoaffective patient-subjects.[70] The preference of BPD patients for "eveningness" (including delayed sleep timing and difficult morning awakening) rather than "morningness" suggests a rather stable chronotype. However, this chronotype varies somewhat seasonally and with shorter light cycle duration during fall-winter phases.[39]

Actigraphy has also documented reduced total activity[56,71-73] and blunted daily activity-amplitude in MDD subjects,[74] sometimes with circadian phase advances in

subjects with endogenous depression.[75] Such alterations have been particularly striking among subjects diagnosed with bipolar disorder during mania, depression, or shortly before or after acute episodes of illness, as well as in mild or subsyndromal morbid phases.[76-82] Some changes persist after clinical recovery from depression or mania, and so may serve as biomarkers of stable traits, and not only as covariates of current mood states.[74,83]

Phase-advances of circadian motility cycles in BPD depression and mania also usually paralleled similar phase-shifts of other circadian rhythms, including body temperature, blood pressure, pulse rate, urine volume, norepinephrine metabolism, and hormone secretion (eg, cortisol), as well as sleep.[84,85] BPD patients also show *persistent* dysregulation of other rhythmic autonomic functions as well (notably, reduced heart-rate variability) independent of drug treatments.[86]

Sleep monitoring (polysomnography) has shown shortened latency from onset of sleep to the first rapid eye-movement (REM) phase in both major depression and mania, greater inter-night variability of sleep duration and increased nocturnal time awake, with delayed sleep onset and longer sleep duration in remitted BPD outpatients compared with matched, healthy controls,[84] as well as impaired sleep efficiency and disruption of circadian activity patterns in euthymic BPD patients versus controls with or without insomnia.[62,82,87]

Such abnormalities may be associated with the emerging evidence that longevity is reduced among BPD patients (reflected as a huge excess of deaths owing to suicide or other violence in the young, and a moderate, but important increase in mortality due to cardiovascular, pulmonary, and other medical illnesses in older patients).[88,89] Such findings suggest that some physiological characteristics may be relatively enduring "trait-makers," diagnostic features, or potential endophenotypes, and not merely nonspecific abnormalities associated with emotional distress, acute illness, or treatment effects. Notably, systematic abnormalities in acrophase-timing, with sustained *phase-advances*, support the hypothesis that circadian rhythms of BPD patients cycle somewhat faster than once every 24 hours.[90] Mood-stabilizing treatment with lithium can slow circadian motility rhythms and promote more nearly normal 24-hour cycles.[91] In SAD patients, bright-light therapy may normalize circadian rhythms, and dawn-simulation can facilitate awakening, consistent with phase-delay hypothesis for seasonal mood disturbances.[66]

Also, melatonin, regulated by the environmental light/dark cycle, can act as an endogenous synchronizer, either in stabilizing or reinforcing bodily rhythms. It is therefore called a "chronobiotic" molecule or zeitgeber involved in signaling the time of day and time of year.[92] Phase-shifting by melatonin has been attributed to actions on brain melatonin MT2 receptors present in the hypothalamic suprachiasmatic nucleus (SCN) that directly influence the electrical and metabolic activity of this critical nucleus.[92] In addition to its phase-shifting effect, melatonin acts directly on the amplitude of daily oscillations in activity and other rhythms. Of interest, reduced or blunted amplitude of melatonin secretion was found in depressive BPD patients during clinical recovery, and low melatonin levels may represent a trait marker for depression.[93] In an attempt to take advantage of the therapeutic opportunities available through the central melatonin system, researchers have developed several melatonin agonists with improved properties over those of melatonin itself.[94-97]

Nonlinear dynamic approaches

Developing appropriate models to describe patterns of mood instability in mood disorders is important because modeling can guide specific investigations and treatment strategies. Chief among current models for describing mood instability in bipolar disorder (BPD) in particular, consider disruption of biological rhythms and kindling. Biological rhythm modeling has been encouraged by the observation of 48-hour, manic-depressive mood cycles in some BPD patients to suggest intrinsic periodicity and disturbance of endogenous, perhaps circadian, biological rhythms.[20,98] The kindling hypothesis is based on some evidence that episodes may become more frequent and more spontaneous or autonomous as BPD progresses.[99] However, other findings tend to refute the model of progressive worsening or declining treatment-responses in BPD.[100-102]

It is difficult to invoke either of these models to explain the irregular pattern of mood fluctuation seen in long-term mood records obtained from outpatients under naturalistic observation. Specifically, inspection of such records provides evidence that regularly cyclic mood patterns are uncommon and, when they do occur, are short-lived. Nevertheless, visual inspection of clinical records suggests that mood patterns in BPD patients, although lacking regular or consistently progressive peri-

odicity, may be more organized than those of normal subjects. Mood records of BPD patients, indeed, might be described in terms of chaotic process using principles of nonlinear dynamics.[102] Although, chaos generally implies disorder, it is also a term used to describe apparently random behavior by a deterministic system in the theory of nonlinear dynamics.[103] An important implication of this distinction between chaos and random processes is that complex-appearing chaotic behavior can be described by relatively simple mathematical models whereas the mathematic description of truly random processes requires an infinite number of dimensions.

The ability to represent the behavior of a process with few dimensions suggests that the behavior originates from a process with extraordinarily complex dynamics. Although the increased degree of temporal organization of mood in BPD patients compared with normal controls may seem counterintuitive, such an interpretation accords with experimental observations, in which pathological states were marked by degrees of organization that reflect a low-dimensional chaotic process. Whether such finding represents neural processes that are latent in normal controls and become dominant in pathological states including BPD, or whether they represent the emergence of a new, qualitatively distinct process has not been determined.

The complex relationship of external stressors to mood in BPD may also be accounted for by a model based on a low-dimensional chaotic process. An appropriately timed psychosocial stressor may exacerbate symptoms by driving a pathologically configured system to transient or sustained pathologic dynamics. In this way, a stressor may produce long-lasting effects on mood, producing many episodes apparently unlinked to any stressor, rather than being linked in a simple stimulus-response fashion to a single episode. This possibility may also explain why it has been reported to be more difficult to associate later episodes in BPD with discrete, identifiable stressors—an important assumption for the kindling model.[99] Such trends, if valid, would seem to indicate that long-term mood changes in BPD patients, although not cyclic, are still highly organized compared with normal controls, and can be characterized by the presence of a low-dimensional chaotic process. Traditional steady-state or simple oscillatory models of mood disorders cannot account for such findings. Consequently, the study of more dynamically complex oscillatory systems is required to understand the relevant pathogenic mechanisms and perhaps pointing toward new, dynamically oriented treatment strategies.[104]

Heiby and colleagues noted that mood fluctuations in chronically depressed persons were more regular than those observed in healthy subjects.[105] This finding led to the maladaptive determinism hypothesis which associated illness with regularity or low complexity, and health with high complexity and more noise.

Additional analysis using the methods in nonlinear dynamics led to different multi-scale structure in the activity data. Recent study on probability distributions of human activity signals revealed a universal distribution with a long tail.[106] Regardless of the individual's daily activity, exogenous conditions, phase of the circadian rhythm and average activity, there exists an invariant structure. These distributions of activity data obtained from healthy controls collapse to a universal distribution. However, alteration in the probability distribution of the activity has been reported for patients with depression and for such patients the characterizing parameter of the probability distribution is significantly lower than in healthy controls.[106] Scaling behavior of amplitudes at multiple timescales of activity data has also been reported[107] and such behavior distinguished patients with bipolar disorder from healthy controls. In addition characterizing parameters of the scaling behavior are found to be correlated with the suicidal thinking in MDD.[108]

Conclusion

The present article has come about as a sort of "diary" of the scientific journey that the authors started as collaborators some years ago. At that time, from the improbable encounter between a mathematician-engineer, a psychologist, and two psychiatrists, studying nonlinear dynamics in actigraphy-monitoring data of mood disorders patients sprang a fertile intellectual dialogue between persons with highly diverse research backgrounds and somewhat distant cultural avenues that has led to the conclusion that the integration of various conceptual models and theoretical frameworks can shed light on unresolved research questions.

The archetype Kronos-Saturn and its philosophical association with melancholic states give the frame of reference that time and temporality are not only a dimension of coexisting opposite and contradictory forces or a realm of changing, flowing, or fluctuating features but

also constitute a dimension that "devours its children and hides them, as it were, in a black hole," thus manifesting as a hidden realm of static and deterministic annihilation, as a lack of motion and "becoming." Also, phenomenology and subjective psychopathology as well as Nietzsche's thought problem indicate that extremely severe mood conditions such as Cotard's and psychotic mania, ie, Superman syndromes, are indeed meaningful representations of this existential paralysis/annihilation of lived time.

Pychopathology and phenomenology of subjective experience of lived time in mood disorders have also focused on the broad range of dynamic elements of temporal perception and have linked temporality disturbances to psychomotor activity, vitality and physical vigor as well as drive. Circadian research protocols concern the more visible side of temporal organization, whereas the nonlinear dynamics explore further the hidden dimensions of temporality in affective disorders, its structure at multiple time scales. ❑

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Ritmos biológicos y trastornos del ánimo

La integración de algunas aproximaciones relacionadas con el tiempo y la temporalidad pueden mejorar el estudio fisiopatológico de los trastornos del ánimo de etiología desconocida. Se propone que estas condiciones podrían ser interpretadas como trastornos del perfil temporal de los ritmos biológicos, así como alteraciones en la conciencia del tiempo. Algunas aproximaciones útiles para estudiar el tiempo y la temporalidad incluyen propuestas filológicas, conceptualizaciones fenomenológicas y psicopatológicas, descripciones clínicas e investigación de los ritmos circadianos y ultradianos, como también aproximaciones dinámicas no lineales para sus análisis.

Rythmes biologiques et troubles de l'humeur

L'intégration de plusieurs modalités concernant le temps et la temporalité peut améliorer la connaissance physiopathologique de la plupart des troubles de l'humeur d'étiologie inconnue. Nous proposons que ces pathologies soient interprétées comme des troubles du profil chronologique des rythmes biologiques, ainsi que des altérations de la conscience du temps. Des suggestions philologiques, des conceptualisations phénoménologiques et psychopathologiques, des descriptions cliniques et la recherche sur les rythmes circadiens et ultradiens, ainsi qu'une approche dynamique non linéaire de leur analyse sont des moyens utiles pour étudier le temps et la temporalité.

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