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Real-time Mobile Monitoring of the Dynamic Associations Among Motor Activity, Energy, Mood, and Sleep in Adults With Bipolar Disorder

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IMPORTANCE Biologic systems involved in the regulation of motor activity are intricately linked with other homeostatic systems such as sleep, feeding behavior, energy, and mood. Mobile monitoring technology (eg, actigraphy and ecological momentary assessment devices) allows the assessment of these multiple systems in real time. However, most clinical studies of mental disorders that use mobile devices have not focused on the dynamic associations between these systems.

OBJECTIVES To examine the directional associations among motor activity, energy, mood, and sleep using mobile monitoring in a community-identified sample, and to evaluate whether these within-day associations differ between people with a history of bipolar or other mood disorders and controls without mood disorders.

DESIGN, SETTING, AND PARTICIPANTS This study used a nested case-control design of 242 adults, a subsample of a community-based sample of adults. Probands were recruited by mail from the greater Washington, DC, metropolitan area from January 2005 to June 2013. Enrichment of the sample for mood disorders was provided by volunteers or referrals from the National Institutes of Health Clinical Center or by participants in the National Institute of Mental Health Mood and Anxiety Disorders Program. The inclusion criteria were the ability to speak English, availability to participate, and consent to contact at least 2 living first-degree relatives. Data analysis was performed from June 2013 through July 2018.

MAIN OUTCOMES AND MEASURES Motor activity and sleep duration data were obtained from minute-to-minute activity counts from an actigraphy device worn on the nondominant wrist for 2 weeks. Mood and energy levels were assessed by subjective analogue ratings on the ecological momentary assessment (using a personal digital assistant) by participants 4 times per day for 2 weeks.

RESULTS Of the total 242 participants, 92 (38.1%) were men and 150 (61.9%) were women, with a mean (SD) age of 48 (16.9) years. Among the participants, 54 (22.3%) had bipolar disorder (25 with bipolar I; 29 with bipolar II), 91 (37.6%) had major depressive disorder, and 97 (40.1%) were controls with no history of mood disorders. A unidirectional association was found between motor activity and subjective mood level (β = −0.018, P = .04). Bidirectional associations were observed between motor activity (β = 0.176; P = .03) and subjective energy level (β = 0.027; P = .03) as well as between motor activity (β = −0.027; P = .04) and sleep duration (β = −0.154; P = .04). Greater cross-domain reactivity was observed in bipolar disorder across all outcomes, including motor activity, sleep, mood, and energy.

CONCLUSIONS AND RELEVANCE These findings suggest that interventions focused on motor activity and energy may have greater efficacy than current approaches that target depressed mood; both active and passive tracking of multiple regulatory systems are important in designing therapeutic targets.

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Author Audio Interview

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The role of physical activity in human health has received increasing attention in both medicine and public health. Physical activity is associated with numerous human functional processes, including cognition, sleep, and weight regulation[1,2]; in contrast, low physical activity is increasingly recognized as a risk factor for diabetes,[3] cardiovascular disease,[4] cancers,[5,6] and mental disorders.[7,8] Mobile monitoring, which allows simultaneous, frequent, and reliable assessment of multiple systems in real time, has provided new opportunities for obtaining an objective assessment of physical activity.

Patterns of motor activity are assessed through actigraphy, in which a wrist-worn device provides objective and high-density measurements of physical movement in natural living environments.[9] Actigraphy has been used primarily to derive objective measures of sleep characteristics,[10,11] but interest in 24-hour patterns of motor activity,[12] sedentary behavior,[13] physical activity or exercise,[14] and weight regulation[15] has been increasing. With the recent growth in the use of actigraphy, data are now available from several large population-based studies[14,16-18] and from studies of specific conditions, such as diabetes[3,19] and cardiovascular disease.[20,21] In addition, there has been a resurgence of the use of actigraphy to assess physical activity in people with mental disorders, including mood disorders,[22,23] schizophrenia,[24] attention deficit disorder,[25] and posttraumatic stress disorder.[26] Consistent evidence now exists for the dysregulation of motor activity in people with bipolar disorder.[27-32]

Basic research has shown that the biologic systems involved in the regulation of motor activity are associated with other homeostatic systems such as sleep, feeding behavior, energy, and mood.[32,33] For example, shared circuits have been shown to affect sleep and metabolic systems,[34] sleep and feeding behavior,[35] and motor activity and metabolism or energy.[36,37] However, most clinical research in mental disorders that uses mobile devices has focused on either sleep or motor activity rather than on the associations between them. Moreover, a key challenge lies in associating these objectively measured systems with the subjective psychological states that remain central to mental disorders, particularly mood and cognitive experience. This limitation can be overcome by administering ecological momentary assessment (EMA), which has been widely used to investigate emotional regulation in real time in people with mood and other mental disorders. Furthermore, EMA overcomes the temporal and contextual limitations of traditional clinical measures.[38-44] The concomitant use of both EMA and actigraphy provides a powerful approach to investigating the context of passively acquired data as well as the directional patterns and associations of homeostatic regulatory networks.

The specific aims of this study were to (1) characterize the direction of the associations among activity, energy, mood, and sleep in the natural context of daily life, using a combination of actigraphy and EMA in a community-based sample of adults and youth, and (2) evaluate whether these patterns differ in people with a history of bipolar disorder or major depression compared with controls (people without bipolar or major depression). Our hypothesis was that people with bipolar I disorder have greater sensitivity to changes in homeostatic networks as indexed by greater directional associations among activity, energy, mood, and sleep.

Key Points

Question What are the dynamic associations among motor activity, energy, mood, and sleep, as tracked in real time with mobile monitoring technology, in individuals with a history of bipolar disorder or major depression?

Findings In this case-control study of 242 adults, bidirectional associations were found between motor activity with subjectively rated energy level and sleep duration as well as unidirectional associations between motor activity and mood level. Greater cross-domain reactivity was observed for these associations in people with bipolar I disorder.

Meaning Interventions that target motor activity and energy may alleviate depressed mood more effectively than could current approaches; simultaneous investigations of multiple regulatory systems in bipolar disorder are important in designing therapeutic targets.

Methods

Study Design and Sample

This study used a nested case-control design and involved a community-based sample of 242 adults. Probands were recruited from the greater Washington, DC, metropolitan area from January 2005 to June 2013. Enrichment of the sample for mood disorders was provided by volunteers or referrals from the National Institutes of Health Clinical Center or participants in the National Institute of Mental Health Mood and Anxiety Disorders Program. The community sample, designed to be a nontreatment or nonclinical group with and without mental health disorders, was ascertained by mail contact; the addresses were obtained from a marketing list of households within a 50-mile radius of Washington, DC. Inclusion criteria were the ability to speak English, availability to participate, and consent to contact at least 2 living first-degree relatives. Additional details of the family study methods are described in Merikangas et al.[45] All participants provided written informed consent, and the study was approved by the Combined Neuroscience Institutional Review Board at the National Institutes of Health. Data analysis was performed from June 2013 through July 2018.

The sample included 242 adults, all of whom were evaluated at the National Institutes of Health Clinical Center.[45] Other characteristics of the subsample who participated in actigraphy monitoring and EMA rating are presented in previous publications.[46,47]

Measures

DSM-IV mood disorder diagnoses were based on semistructured diagnostic interviews. The controls (n = 97) had no lifetime history of mood disorders. Actigraphy monitors (Respironics and Actiwatch Score; Philips Respironics), which

collect minute-by-minute activity counts, were worn by participants on their nondominant wrist for 2 weeks.

Data on sleep duration (sleep and wake-up times) were obtained from the actigraphy monitor. Wake and sleep periods were defined by a default threshold of fewer than 40 counts per period for more than 10 minutes. This threshold setting has been shown to provide a reliable discrimination between sleep and wake periods, when validated against polysomnography.[48]

Along with wearing an actigraphy device, participants completed EMAs 4 times per day, with an approximately 4-hour delay between assessments, for 2 weeks. Because the comprehensive superiority of fixed over random assessments has not been established and empirical findings are similar for both approaches,[49,50] fixed intervals were chosen for the present study to facilitate the examination of rhythms and routines, which are more accurately characterized when individuals describe their specific behaviors at the same time over a number of days. The EMA included separate 7-point Likert scales to measure the degree to which participants felt very happy (1) to very sad (7) as well as very tired (1) to very energetic (7). These questions were administered through a personal digital assistant (Tungsten E2 PDA; Palm) provided to participants for the duration of the study. Since 2013, the EMA has been administered on an Android platform. Participants were compensated for their completion of the EMA and actigraphy per standard institutional review board procedures.

Statistical Analysis

Outcome Variables

The original 7-level measures of mood and energy were centered around the group median, the median of measures at that same time of the day across all participants and all days; therefore, mood and energy variables indicate deviations from the diurnal sample median. The mean activity counts between each of the EMA assessments were calculated and then transformed using the Box-Cox method to accommodate for skewed data. The transformed mean activity variables were then centered by the group mean across all participants and all days at that same time.

Covariates

Age, sex, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and use of medications for mood disorders (antidepressants, mood stabilizers, anxiolytics) that have been associated with physical activity were included as covariates in the models. In the analyses of physical activity and psychological states (mood and energy), we controlled for total sleep duration of the previous night. Weekday and weekend status were also controlled because of the large differences in the key outcome variables. Because no change in the estimates was observed after controlling for medication use, this variable was not included in the final models.

Missing Data

Based on established procedures for EMA data, the start day of mobile monitoring assessments was random to avoid systematic bias in missing data by day of the week. No statistically significant *fatigue effect*, defined as increases in missing EMA or actigraphy data as a function of day of the study, was observed. No group differences were found in the percentage of missing data for EMA.

Statistical Methods

Generalized estimating equation models were used to make a conditional estimate of the dynamic association among motor activity, sleep, and psychological states while accounting for the lagged associations of various systems. We included the 3 mood disorder subtypes (bipolar I, bipolar II, and major depression) as binary variables in the generalized estimating equation models, and all other covariates (including sex, age, BMI, and medication use) were the independent variables. The reference group for each mood disorder subtype was the control group without a history of mood disorder. We employed deviations from diurnal medians as the primary measure because the population-level diurnal patterns observed in the key study variables violate a key assumption (stationarity) of Granger causality models. The first-order autoregressive working correlation structure was chosen to take into account the within-person correlation over the 2-week observation period. Wald χ^2 test was used to test the significance of each variable and their respective 2-sided P values at the $\alpha = .05$ level. All analyses were conducted using SAS, version 9.3 (SAS Institute Inc).

Results

Of the total 242 participants, 92 (38.1%) were men and 150 (61.9%) were women, with a mean (SD) age of 48 (16.9) years. Among the participants, 54 (22.3%) had bipolar disorder (25 with bipolar I; 29 with bipolar II), 91 (37.6%) had major depressive disorder, and 97 (40.1%) were controls with no lifetime history of mood disorders.

Prospective Association of Motor Activity on Subsequent Mood and Energy

Table 1 presents the prospective association of motor activity with subsequent subjective mood (top) and energy (bottom) levels in the total sample as well as the associations with mood disorder subtype compared with controls. After controlling for sex, age, BMI, weekday vs weekend status, and status of the outcome in the previous assessment, we found a statistically significant inverse association between observed activity in one period and sad mood level in the next period ($\beta = -0.018$; $P = .04$) as well as a positive association between activity and energy level in the next period ($\beta = 0.027$; $P = .03$). Sad mood levels decreased with age and were lower on weekends compared with weekdays ($\beta = 0.10$; $P < .001$). Actigraphy-estimated sleep duration from the previous night was associated with motor activity in the energy-predicting activity model ($\beta = -0.154$; $P = .04$) but not in the mood-predicting motor activity model ($\beta = -0.131$; $P = .06$), or with mood ($\beta = 0.009$; $P = .51$) or energy ($\beta = 0.022$; $P = .36$) level on the next day. Models that tested the interactions between the mood disorder subtypes and activity yielded significant interactions be-

Table 1. Lagged Associations Between Motor Activity on Mood (Top) and Energy (Bottom)

Category	Estimate	*P* Value
Outcome: Mood$_t$[a]		
Motor activity$_{t-1}$[b]	−0.018	.04[c]
Mood disorder subtype		
Bipolar I	0.125	.09
Bipolar II	0.167	.03[c]
Major depression	0.026	.63
Interactions		
Activity$_{t-1}$ × bipolar I	−0.035	.03[c]
Activity$_{t-1}$ × bipolar II	−0.007	.67
Activity$_{t-1}$ × major depression	0.012	.41
Model covariates		
Age	−0.003	.049[c]
Sex (F vs M)	−0.047	.36
Body mass index	0.005	.19
Mood$_{t-1}$	0.675	<.001[c]
Sleep duration, h	0.009	.51
Weekday	0.100	<.001[c]
Outcome: Energy$_t$[d]		
Motor activity$_{t-1}$	0.027	.03[c]
Mood disorder subtype		
Bipolar I	−0.145	.17
Bipolar II	0.005	.97
Major depression	−0.073	.39
Interactions		
Activity$_{t-1}$ × bipolar I	0.062	.004[c]
Activity$_{t-1}$ × bipolar II	0.006	.82
Activity$_{t-1}$ × major depression	−0.010	.64
Model covariates		
Age	0.002	.38
Sex (F vs M)	−0.144	.07
Body mass index	0.001	.84
Energy$_{t-1}$	0.411	<.001[c]
Sleep duration, h	0.022	.36
Weekday	−0.030	.42

Abbreviations: F, female; M, male; t, period; t-1, same domain in previous period (Granger model).

[a] Analog mood scale rated by participant 4 times per day for 2 weeks.

[b] Mean counts per minute for each period.

[c] Denotes statistically significant finding.

[d] Analog energy scale rated by participant 4 times per day for 2 weeks.

Table 2. Lagged Associations Between Mood (Top) and Energy (Bottom) on Motor Activity

Category	Estimate	*P* Value
Outcome: Motor Activity$_t$[a]		
Mood$_{t-1}$[b]	−0.099	.23
Mood disorder subtype		
Bipolar I	−0.397	.28
Bipolar II	0.383	.28
Major depression	−0.017	.95
Interactions		
Mood $_{t-1}$ × bipolar I	−0.382	.07
Mood $_{t-1}$ × bipolar II	−0.019	.91
Mood $_{t-1}$ × major depression	−0.151	.33
Model covariates		
Age	−0.041	<.001[c]
Sex (F vs M)	0.292	.29
Body mass index	−0.063	<.001[c]
Activity$_{t-1}$	0.416	<.001[c]
Sleep duration, h	−0.131	.06
Weekday	−0.126	.25
Outcome: Motor Activity$_t$[a]		
Energy$_{t-1}$[d]	0.176	.03[c]
Mood disorder subtype		
Bipolar I	−0.295	.43
Bipolar II	0.328	.35
Major depression	0.021	.94
Interactions		
Energy $_{t-1}$ × bipolar I	0.360	.056
Energy $_{t-1}$ × bipolar II	−0.148	.49
Energy $_{t-1}$ × major depression	0.021	.87
Model covariates		
Age	−0.041	<.001[c]
Sex (F vs M)	0.366	.19
Body mass index	−0.066	<.001[c]
Activity$_{t-1}$	0.413	<.001[c]
Sleep duration, h	−0.154	.04[c]
Weekday	−0.219	.04[c]

Abbreviations: F, female; M, male; t, period; t-1, same domain in previous period (Granger model).

[a] Mean counts per minute for each period.

[b] Analog mood scale rated by participant 4 times per day for 2 weeks.

[c] Denotes statistically significant finding.

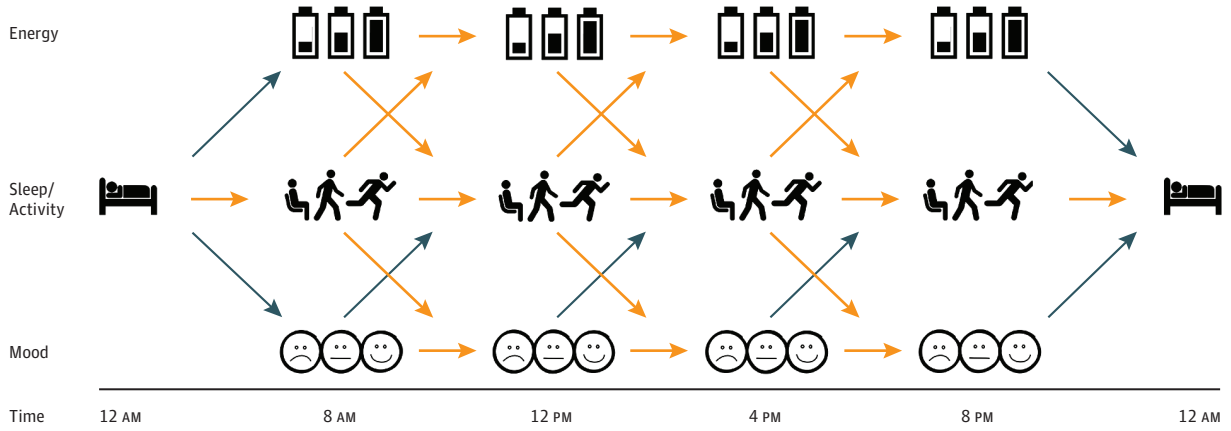
[d] Analog energy scale rated by participant 4 times per day for 2 weeks.

tween motor activity and bipolar I disorder on both mood (β = -0.035; *P* = .03) and energy (β = 0.062; *P* = .004) levels. Specifically, increased activity was associated with greater changes in mood, energy, and sleep duration among those with bipolar I disorder compared with controls. No interactions emerged for the other 2 mood disorder subtypes.

Prospective Associations of Mood and Energy on Subsequent Motor Activity

Table 2 presents the results of prospective analyses that evaluated the associations of subjective mood and energy with subsequent motor activity. Greater subjective energy (β = 0.176; *P* = .03) but not mood (β = -0.099; *P* = .23) level was associated with a subsequent increase in activity. Activity levels did not differ substantially by mood disorder subtype, but they were negatively associated with age; BMI; and, in the models with energy as an outcome, previous night sleep duration and weekday status. There was a trend for an interaction between mood and energy levels and activity in the subsequent period among those with bipolar I disorder, who exhibited a greater decrease in activity after increases in sad mood (β = -0.382; *P* = .07) and a greater increase in activity after increases in energy level (β = 0.360; *P* = .056).

Figure. Summary of Within- and Across-Domain Associations of Subjective Mood and Energy, Motor Activity, and Sleep Duration



Subjective energy and mood were assessed by ecologic momentary sampling and motor activity, and sleep duration was assessed by actigraphy across 2 weeks. Yellow (thicker) arrows indicate statistically significant associations; blue arrows indicate nonsignificant associations.

Increased activity, but not energy or mood, was associated with less sleep on the subsequent evening (data not shown). Similar to other domains, an interaction was observed between bipolar I disorder and sad mood level and subsequent sleep duration: Higher sad mood level was associated with increased sleep duration in those with bipolar I disorder but decreased sleep duration in controls.

Directional Associations Among Sleep, Energy, Activity, and Mood

The **Figure** summarizes the directional associations of the time-lagged estimates of energy, activity, mood, and sleep over a 24-hour period in the total sample, based on the analyses presented in Tables 1 and 2. First, strong associations were observed within each domain (energy, activity, mood) over the course of the day. Second, cross-domain, bidirectional associations were found between energy level (β = 0.027; *P* = .03) and motor activity (β = 0.176; *P* = .03) as well as between sleep duration (β = -0.154; *P* = .04) and motor activity (β = -0.027; *P* = .04). Third, a unidirectional association was seen between motor activity and subsequent changes in mood (β = -0.018; *P* = .04), but mood levels were not associated with either subsequent activity or sleep level. Increased sleep duration on the previous night was associated with decreased activity on the next day, and decreased activity during the day were associated with increased sleep duration on the next evening. No direct associations were observed between mood or energy level and sleep duration on the next evening or the converse.

Discussion

Using mobile monitoring (actigraphy and EMA devices) and traditional clinical methods, we examined the highly dynamic interplay of multiple brain-body systems involved in the homeostatic regulation of human energy, mood, motor activity, and sleep. Results revealed a unidirectional association of motor activity with mood and bidirectional association of motor activity with subjective energy and sleep duration. Findings regarding the central role of motor activity patterns in mood regulation and the salience of subjective energy as a primary factor in motor activity suggest that motor activity may be a more malleable behavioral target of intervention than mood. Our application of fragmentation analysis, a novel statistical technique, to a study of the stability of these domains revealed greater instability of energy and attention, but not mood, in people with bipolar I disorder compared with controls.[51] Greater cross-domain reactivity in bipolar I disorder further implicates the lack of central coordination of the network of motor activity, sleep, mood, and energy rather than the dysregulation of any single domain. Failure to consider changes in perturbations of different systems within these networks that drive or maintain set points of equilibrium may actually lead to greater resistance to change in related systems.[52] The lack of integration among weight,[53] sleep,[54] and mood disorders[55] may help explain the lack of enduring effectiveness of most intervention programs, which generally focus on only 1 of these domains.

The unidirectional associations of motor activity with depressed mood suggest that novel pharmacologic, physical, and behavioral therapeutic approaches focused on increasing energy and activity (eg, norepinephrine bitartrate, hypocretin/orexin, dopaminergic systems as targets) may be more effective than current treatments that target mood elevation or stabilization in bipolar disorder and major depressive disorder. The success of monoamine oxidase inhibitors in treating low energy in the atypical subtype of depression, which is often associated with bipolar disorder, may be attributable to their stimulating effects on energy and activity rather than mood.[56] In addition, consideration of intrinsic rhythms in the timing of interventions,[35,57] such as pharmacologic (eg, melatonin-based interventions)[58] and/or behavioral interventions designed to enhance circadian rhythmicity,[59,60] may be more effective than interventions in one of these domains alone.[55,61]

Our findings of the central role of motor activity patterns,[23,30] the salience of subjective energy as a primary disturbance in motor activity,[62] and the increased cross-domain reactivity across regulatory systems in bipolar I disorder also provide a model for translational research. More insight has emerged into the molecular biologic mechanisms underlying rhythms of sleep, activity, and eating[63] as well as the role of circadian regulation of human physiologic systems[57,64-66] and diseases.[64,67,68] Basic science research could, therefore, examine whether disturbances in the coordination of hypothalamic regulatory systems, such as regulatory hypocretinergic systems and their catecholaminergic modulation,[69,70] may underlie the increased cross-system reactivity observed in people with bipolar I disorder in this study. Greater understanding of the directions and mechanisms for these associations could explain how motor activity; sleep; eating; mood; cognition; and their underlying neural, physiologic, and molecular processes affect energy, interact in more complex networks, and help identify targets for intervention.

Our application of mobile monitoring in a community-based sample with a broad age range illustrates the feasibility of real-time in vivo active and passive assessment techniques.[10,71] The joint application of passive data from actigraphy and active responses from EMA to improve the characterization of mental disorders demonstrates the central role of subjective psychological states, such as energy and mood, in bipolar disorder.[72] The use of community sampling with clinical enrichment in this investigation extends the approach in previous research, which has generally been restricted to clinical convenience sampling that reflects more severe cases and may not be representative of mood disorders in the general population. Another strength of the present study is its analytic approach: (1) it incorporates covariates, such as BMI, diurnal stationarity, and weekend vs weekday factors, that may have confounded previous analyses, and (2) it employs Granger causality in the context of multilevel models to examine directional cross-domain associations.

Limitations

This study has limitations. First, we initially used 2-week cross-sectional measures of the key study domains. We are now repeating these assessments over longer periods and multiple times per year to study the generalizability of these findings over time. Second, we used actigraphy-based sleep assessment, which is only an index of sleep duration. However, our methods do conform with recommendations for actigraphy procedures recommended by the Society of Behavioral Sleep Medicine.[11] Third, we analyzed only a subset of domains involved in these complex homeostatic networks and did not include measures of eating, stress, light, or other extrinsic factors in the core domains evaluated in this study. Future research into these networks could be enhanced by the inclusion of biologic correlates of the daily measures and the use of newer devices that measure light; temperature; and other metabolic correlates of motor activity, sleep, and mood.[73] Light exposure is particularly critical because of its association with sleep, mood, and daily rhythms documented in basic science[74] and because of the advantages of light treatment for humans shown in early pioneering studies[75-79] and more recent applications.[80,81] Moreover, low levels of light exposure during early childhood have even been postulated as a potential risk factor for the development of bipolar disorder.[82]

The simultaneous study of fluctuations in multiple systems that mimic real-life homeostatic regulation will require larger samples than can be collected at any site. For this reason, we have established a collaborative international consortium, the Motor Activity Research Consortium for Health (mMARCH),[30] to enhance the ability to examine the generalizability of the present findings (with respect to state vs trait, sex differences, subgroups of mood disorders, and geographic and seasonal variations) and to extend this work to other mental and general health conditions. We are now comparing these earlier data with more recent data from other devices for actigraphy (GENEActiv, www.activinsights.com) and smartphones for EMA on a larger number of participants across collaborating sites.

Conclusions

The cross-domain reactivity in bipolar disorder highlights the importance of identifying potential mechanisms for the lack of synchrony across specific domains as well as the need for tracking multiple regulatory systems in identifying therapeutic targets. The application of real-world mobile technology to track human behavior and physiologic function in real time, coupled with advances in circadian medicine[83] and molecular biologic systems research,[63] provides unprecedented opportunities for increasing our understanding of the regulation of the core features of mood and other disorders, allowing us to gain insights into their underlying biologic, genetic, and environmental mechanisms and to define novel targets for intervention. Our findings also underscore the importance of both objective and subjective data that provide complementary information needed for fully characterizing these complex systems.

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Conflict of Interest Disclosures: Prof Hickie reported being the 2012-2018 commissioner of Australia's National Mental Health Commission; being a codirector of Health and Policy at the Brain and Mind Centre, University of Sydney; leading community-based and pharmaceutical industry–supported (Wyeth, Eli Lily, Servier, Pfizer, and AstraZeneca) projects focused on the identification and better management of anxiety and depression; being a member of the Medical Advisory Panel for Medibank Private until October 2017; being a board member of Psychosis Australia Trust and a member of the Veterans Mental Health Clinical Reference group; and being the Chief Scientific Advisor to and an equity shareholder in Innowell. No other disclosures were reported.

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