Covariation of Depressive Mood and Spontaneous Physical Activity in Major Depressive Disorder: Toward Continuous Monitoring of Depressive Mood

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***Abstract*—The objective evaluation of depressive mood is considered to be useful for the diagnosis and treatment of depressive disorders. Thus, we investigated psychobehavioral correlates, particularly the statistical associations between momentary depressive mood and behavioral dynamics measured objectively, in patients with major depressive disorder (MDD) and healthy subjects. Patients with MDD ($n = 14$) and healthy subjects ($n = 43$) wore a watch-type computer device and rated their momentary symptoms using ecological momentary assessment. Spontaneous physical activity in daily life, referred to as locomotor activity, was also continuously measured by an activity monitor built into the device. A multilevel modeling approach was used to model the associations between changes in depressive mood scores and the local statistics of locomotor activity simultaneously measured. We further examined the cross validity of such associations across groups. The statistical model established indicated that worsening of the depressive mood was associated with the increased intermittency of locomotor activity, as characterized by a lower mean and higher skewness. The model was cross validated across groups, suggesting that the same psychobehavioral correlates are shared by both healthy subjects and patients, although the latter had significantly higher mean levels of depressive mood scores. Our findings suggest the presence of robust as well as common associations between momentary depressive mood and behavioral dynamics in healthy individuals and patients with depression, which may lead to the continuous monitoring of the pathogenic processes (from healthy states) and pathological states of MDD.**

***Index Terms*—Depressive mood, ecological momentary assessment (EMA), locomotor activity, major depressive disorder (MDD), multilevel modeling.**

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I. Introduction

MAJOR depressive disorder (MDD) is a psychiatric disorder that is characterized by the presence of mood disturbances (either depressed mood or a loss of interest or pleasure in daily activities) consistently for more than several weeks [1]. In addition to these mood disturbances, behavioral alterations, including diminished activity, loss of energy, and psychomotor retardation or agitation, are remarkable cooccurring symptoms [1]. In fact, many epidemiological studies of depressive disorders that used traditional paper-and-pencil self-report assessments have demonstrated the presence of altered physical activity levels [2]–[6], as well as their significant associations with the severity of the diseases [7], [8]. As a more quantitative approach, many studies on MDD have collected continuous measurements of physical activities in daily life using an activity monitor, and demonstrated a variety of behavioral alterations, including lower activity levels during daytime [9]–[12], sleep disturbances [10], [13], and disruption of the circadian rhythm [11], [14], [15], as well as their improvement over the course of clinical treatment [16]. However, these studies mainly focused only on the alterations of physical activity levels or their rhythmicity, and the complete details of dynamical properties, which may contain richer information regarding pathological states, have not been examined.

In this context, recently, we measured the so-called locomotor activity, i.e., the spontaneous physical activity in daily life, in patients with MDD for >1 week, and reported that patients with depression exhibited more intermittent behavioral patterns that were characterized by reduced mean activity levels associated with occasional bursts of locomotor activity compared with healthy subjects [17], [18]. These findings suggest that the statistical properties of intermittent locomotor dynamics can be important and useful objective markers of MDD, and there is a novel possibility of continuously monitoring the pathological states of this disorder based on behavioral dynamics. However, although these studies were successful in providing a biobehavioral marker for MDD based on long-term (>1 week) locomotor activity data, this is not sufficient for continuous monitoring because of the lack of temporal resolution and correlation with symptoms (e.g., subjective depressive mood). To capture rapid changes in pathological states in much shorter time frames (e.g., daily or within-day scales), which may provide important information on clinical conditions or the efficacy of clinical treatments, other types of approaches are required.

TABLE I
PROFILES OF PATIENTS WITH MDD

Patient No.	Gender [male (M)/female (F)]	Age	Employed [yes (Y)/no (N)]	Disease duration (month)	HDRS score (17 items)
1	M	42	Y	135	12
2	M	35	N	7	11.2
3	F	33	N	36	18.5
4	M	37	N	34	10
5	M	33	N	10	12.8
6	M	35	N	19	8.8
7	M	32	N	18	15.5
8	M	26	Y	69	13
9	F	22	N	22	12.4
10	M	33	Y	33	18.1
11	M	29	Y	7	10.8
12	M	38	N	21	13
13	M	40	N	2	16.8
14	M	41	Y	36	13

HDRS: Hamilton depression rating scale.

Therefore, in this study, we investigated the temporal associations between depressive mood and behavioral dynamics in patients with MDD using ecological momentary assessment (EMA) [19], [20]. We particularly examined the manner in which within-individual temporal changes in depressive mood scores covaried with local statistics of the locomotor activity around the recordings of self-reported symptoms. Furthermore, we compared such associations across patients with MDD and healthy subjects. The identification of differences and/or similarities in the psychobehavioral correlates between patients and healthy subjects is considered important because it may provide valuable insights into the pathogenic processes of MDD; thus, leading to the early detection of the disease.

II. METHODS

A. Subjects

The data were acquired from 14 patients with MDD [12 males (M), two females (F); age 34.0 ± 5.7 years; age range 22–42 years] and 43 healthy office workers (43 M, 0 F; 40.7 ± 9.1 years; 23–58 years). The patients with MDD were outpatients of the Teikyo University Mizonokuchi Hospital, Kanagawa, Japan, and their locomotor activity data have been published elsewhere [17], [18]. The patients who applied for participation in the study were interviewed, and screened using the miniinternational neuropsychiatric interview (MINI) [21] by a well-trained psychiatrist. The inclusion criteria were as follows: a diagnosis of MDD according to the diagnostic and the statistical manual of mental disorders (DSM)-IV [1]; and age between 20 and 55 years. The exclusion criteria were: current substance abuse and other psychiatric diseases; lifetime history of schizophrenia or personality disorder; or severe physical illness. The 17-item Hamilton Depression Rating Scale (HDRS; range: 0–54, no depression: 0–6, mild depression: 7–17, moderate depression: 18–24, severe depression: 25–54) [22] was also administered to all the patients [13.3 (mean) $\pm$ 2.9 (SD); range 8.8–18.5]. The detailed profiles of the patients are summarized in Table I.

The healthy subjects were full-time office workers at the University of Tokyo. They were recruited using the stratified random sampling; we first divided a population into strata (i.e., departments of the university), and, then, took a simple random sample within each stratum. We confirmed that the subjects did not have a past or current psychiatric diagnosis by simply asking them to report whether they have a past or current psychiatric diagnosis or not with a questionnaire. Fifty-three subjects completed their recordings for the entire study period, but we excluded ten subjects who rated a beck depression inventory-II (BDI-II; range: 0–63, minimal or no depression: 0–13, mild depression: 14–19, moderate depression: 20–28, severe depression: 29–63) score of 14 points or more (i.e., clinical cutoff level for depression) [23], [24]. Thus, 43 subjects were analyzed in this study, and the mean score on BDI-II in this group was 5.9 ± 4.0 (range 0–13). In this study, while HDRS was used to monitor pathological states in patients with MDD, BDI-II was used as healthy subjects' baseline test due to practical as well as technical reasons.

All participants in this study were given a full explanation of the purposes and potential risks of the study by well-trained researchers. Subsequently, they signed an institutionally approved informed consent form. This study was approved by the research ethics committees of the Teikyo University and the University of Tokyo.

B. Data Collection

1) Assessment of Self-Reported Symptoms by EMA: We used an EMA technique [19], [20] to record momentary symptoms in patients with MDD and healthy subjects. This approach allows us to address subjects' behaviors, psychological states, and physiological reactions at multiple time points as the individual experiences them in daily life. The collection of data in natural settings can enhance the validity of measurements; thus, avoiding the pitfalls of retrospective recall, which potentially distort self-reported data collection.

A small watch-type computer (Ruputer, ECOLOG, 42 g; Seiko Instruments Inc., Tokyo, Japan) was used as an electronic diary (ED) to record self-reported symptoms [25]–[27]. Patients with MDD were requested to record their momentary symptoms by answering EMA questionnaires over the study period (37.43 ± 14.82 days; range 18–67 days). EMA questionnaires prompted the patients to record their symptoms via a beep signal at randomly selected times within $\pm$36 min of the predefined times (6:00, 12:00, 18:00, and 24:00) during waking periods. Moreover, healthy subjects were instructed to complete the questionnaires at randomly selected times within $\pm$24 min of the predefined times (every 4 h: 8:00, 12:00, 16:00, etc.) during waking periods over seven consecutive days. In addition to these scheduled times, all participants were also requested to register the time at which they woke up or went to bed as well as their momentary symptoms at that time (see Fig. 1). The period of data collection is different between patients with MDD and healthy subjects. The reason for the longer study period in MDD group was that EMA monitoring was performed during their treatment. Also, we used a smaller number of EMA in MDD group to reduce the burden imposed on their treatment.

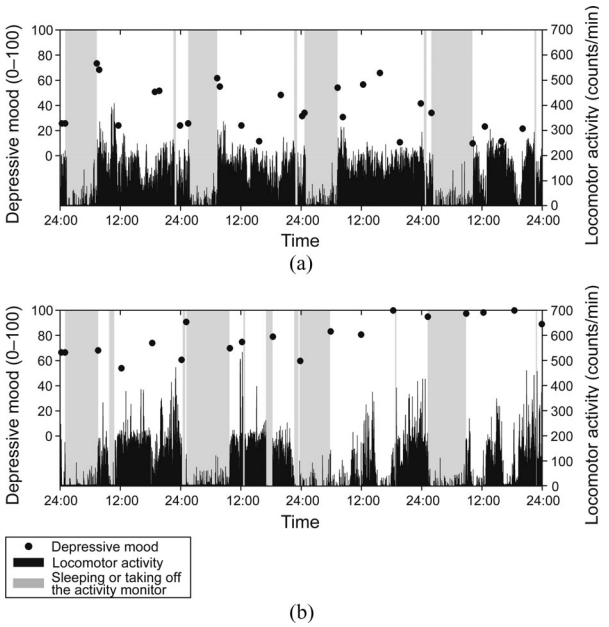

Fig. 1. Fluctuations of depressive mood scores and locomotor activity. Filled circles indicate (a) depressive mood scores (*y*-axis on the left side) recorded by EMA over four consecutive days in a healthy office worker and (b) a patient with MDD. Their locomotor activities simultaneously measured are also shown (*y*-axis on the right side). The periods during which they were sleeping or had taken off the device are shaded in gray.

The EMA questionnaires assessed subjective mood states, and the intensity of physical symptoms (fatigue, sleepiness, pain, etc.) using a visual analog scale (0–100 with 5-point intervals). The mood states were rated using the depression and anxiety mood scale (DAMS) [28], which was developed to measure anxious and depressive moods as separately as possible. DAMS has been shown to possess adequate construct validity compared to the profile of mood states (POMS) in 578 young adults [28]. The correlation between positive mood of DAMS and vigor-activity scale of POMS was 0.61. The correlation between depressive mood of DAMS and depression-dejection scale was 0.67 and that between anxious mood and tension-anxiety scale was 0.65. In addition, the reliability coefficients (Cronbach's alpha) for positive, negative, and anxious moods of DAMS are 0.82−0.89 [28]. The DAMS comprises the following nine adjectives representing mood states: "vigorous," "gloomy," "concerned," "happy," "unpleasant," "anxious," "cheerful," "depressed," and "worried." Based on these items, anxious (sum of "concerned," "anxious," and "worried" scores), positive (sum of "vigorous," "happy," and "cheerful" scores), and negative (sum of "gloomy," "unpleasant," and "depressed" scores) moods were calculated. The depressive mood scores were obtained by combining the last two mood scores [(300 − positive mood score) + negative mood score]. These mood scores were rescaled in the range of 0–100. In this study, we focused on the depressive mood because depressive symptoms are the most prominent feature of MDD, and mood changes are considered as an important sign of the pathogenesis of the disease. In addition, we did not focus on the positive and negative mood of DAMS, because they are subscales for calculating depressive mood. It should also be noted that we confirmed that positive mood is not a robust and unique factor in depressive mood more than the presence of negative mood.

2) Assessment of Locomotor Activity: The watch-type device is also equipped with an activity monitor, which is analogous in performance to the commercial actigraph (Ambulatory Monitors Inc., Ardsley, NY, USA), used widely in the clinical field [11], [17], [18], [26]. The sensor for assessing locomotor activity is a uniaxial piezoelectronic accelerometer capable of detecting small changes in bodily acceleration ($\geq$ 0.01 G/rad/s), which enables to register even slight movements in daily life. All subjects were instructed to wear this device on the wrist of their respective nondominant hand throughout the study period, except while bathing, showering, performing rigorous exercises, or any other activity likely to damage the device. In this study, zero-crossing counts accumulated for every 1 min were used as locomotor activity data (see Fig. 1). Locomotor activity data collected during periods, in which the subjects were not wearing the device or sleeping, were excluded from the analysis.

C. Local Statistics of Locomotor Activity

We focused on the first- and third-order statistical moments (i.e., mean and skewness) of locomotor activity data because the combination of these statistics can well characterize the intermittent or bursty nature of the data. Lower or higher mean activity levels could characterize the states related to psychomotor retardation or agitation, respectively. Positive skewness could quantify the occasional bursts of locomotor activity. Indeed, in our previous study [29], we considered a variety of local statistical indices as a candidate for characterizing the increased intermittency of local locomotor activity, the combination of lower mean levels and higher positive skewness were shown to be effective. While the standard deviation (i.e., the second moment) is a standard measure characterizing variability of given data, it is not appropriate for the case where the data do not obey a normal distribution; the distribution of locomotor activity has nonnegative values leading to a positively skewed distribution. In addition, intermittency or non-Gaussianity in natural phenomena is known to be successfully captured by the higher order statistics, such as nonzero skewness or larger kurtosis (flatness) of the probability distribution of the observed data [30], [31], corresponding to the presence of frequent bursts. Therefore, we modeled the concurrent associations between depressive mood and the local statistical properties of locomotor activity by using the mean and skewness as the statistics that could be robustly calculated from the limited data points (up to 120). These statistics were calculated first from locomotor activity data with a length of 60 min centered around each EMA recording. The effects of the data length (size) and the location against the timing of EMA recording were examined later.

D. Multilevel Modeling

This study produced a hierarchically structured dataset, in which depressive mood scores were measured repeatedly from the same subject during the study period, and, thus, the

corresponding local statistics of locomotor activity were also nested within individuals. Therefore, we adopted a multilevel modeling approach [32]–[34], which is an extension of traditional regression models and has been recommended for the analysis of data with a hierarchical structure, including EMA data [20], [35]. This method can also handle both within- and between-individual effects together in the same model by incorporating random effects into model coefficients, i.e., allowing the coefficients to vary across individuals. All multilevel models were estimated using SAS Proc Mixed (SAS 9.2, SAS Institute Inc., Cary, NC, USA) with the full-information maximum likelihood method [32]. A $p < 0.05$ was considered significant.

1) Descriptive Statistics of Recording Profiles: The mean level of momentary symptoms was estimated using the following null model. In this model, each momentary symptom is the dependent variable with no predictor, including within- and between-individual effects.

Level 1 equation (within-individual level)

$$Y_{ij} = \pi_{0i} + \varepsilon_{ij} \tag{1}$$

Level 2 equation (between-individual level)

$$\pi_{0i} = \gamma_{00} + \zeta_{0i} \tag{2}$$

Combined model

$$Y_{ij} = \gamma_{00} + \zeta_{0i} + \varepsilon_{ij} \tag{3}$$

where Y_{ij} indicates the dependent variable (depressive mood, anxious mood, or fatigue) at the *j*th EMA recording for the *i*th subject; π_{0i} is the subject *i*'s intercept; γ_{00} is the average intercept (i.e., mean level) across all subjects; the random terms ζ_{0i} and ε_{ij} are the between- and within-individual residuals; all variance components were assumed to follow a normal distribution with zero mean. The random term ζ_{0i} represents between-individual effect, indicating that the intercept π_{0i} can vary across individuals.

To test the group differences in mean levels of momentary symptoms, we adopted a two-level mixed MANOVA model [25], [29], which can be modeled by adding a categorical variable representing the type of groups into the right-hand side of (2). Moreover, we performed the same analysis for the local statistics of locomotor activity.

2) Statistical Model for Associations Between Depressive Mood and Locomotor Activity: First, we identified the statistical model that describes the associations between depressive mood scores and the local statistics of locomotor activity using a combined dataset from the healthy and MDD groups. We compared all possible multilevel models that consisted of a linear combination of a subset of both local statistics and their interaction. In addition, we examined both fixed and random effects for each predictor in each model. The specification of considered models is as follows:

Level 1 equation (within-individual level)

$$Y_{ij} = \pi_{0i} + \sum\nolimits_{k=1}^{n} \pi_{ki} X_{ij}^{k} + \varepsilon_{ij} \tag{4}$$

Level 2 equations (between-individual level)

$$\pi_{0i} = \gamma_{00} + \zeta_{0i} \tag{5}$$

$$\pi_{ki} = \gamma_{k0} + \zeta_{ki}\ (k = 1, \ldots, n) \tag{6}$$

Combined model

$$Y_{ij} = \gamma_{00} + \sum\nolimits_{k=1}^{n} \gamma_{k0} X_{ij}^{k} + \zeta_{0i} + \sum\nolimits_{k=1}^{n} \zeta_{ki} X_{ij}^{k} + \varepsilon_{ij} \tag{7}$$

where X_{ij}^{k} is the predictor (local statistics of locomotor activity) corresponding to the *j*th EMA recording for the *i*th subject; *n* is the number of predictors; π_{0i} and π_{ki} are the subject *i*'s intercept and coefficient (i.e., slope) of the predictor, respectively; γ_{00} is the average intercept across all subjects; γ_{k0} is the average slope across all subjects; the random terms ζ_{0i} and ζ_{ki} are the between-individual residuals; and ε_{ij} is the within-individual residual. All variance components were assumed to follow a normal distribution with zero mean. We used the deviance test to compare the goodness-of-fit of the models with nested or inclusive relations, in which all predictors in one model were a subset of the predictors in another model [32].

After identifying the statistical model that best fitted the data, we also examined the robustness of this model against the choice of the data length and temporal location that were used to derive the local statistics of locomotor activity. Particularly, we varied the data length from 10 to 120 min with an increment of 10 min centered around each EMA recording. We also varied the center location of the data from −30 to 30 min of the EMA recording, with the data length set at 60 min.

3) Group Differences in Associations Between Depressive Mood and Locomotor Activity: To examine the differences in the associations between depressive mood scores and the local statistics of locomotor activity across the MDD and healthy groups, we added a categorical variable representing the type of group into the intercept and slopes [i.e., the right-hand side of (5) and (6)] of the model identified.

Level 1 equation (within-individual level)

$$Y_{ij} = \pi_{0i} + \sum\nolimits_{k=1}^{n} \pi_{ki} X_{ij}^{k} + \varepsilon_{ij} \tag{8}$$

Level 2 equations (between-individual level)

$$\pi_{0i} = \gamma_{00} + \gamma_{01} Z_i + \zeta_{0i} \tag{9}$$

$$\pi_{ki} = \gamma_{k0} + \gamma_{k1} Z_i + \zeta_{ki}\ (k = 1, \ldots, n) \tag{10}$$

Combined model

$$Y_{ij} = \gamma_{00} + \gamma_{01} Z_i + \sum\nolimits_{k=1}^{n} \gamma_{k0} X_{ij}^{k} + \sum\nolimits_{k=1}^{n} \gamma_{k1} Z_i X_{ij}^{k} + \zeta_{0i} + \sum\nolimits_{k=1}^{n} \zeta_{ki} X_{ij}^{k} + \varepsilon_{ij} \tag{11}$$

where Z_i is a categorical variable representing a subject's group (i.e., MDD or healthy group).The usage of this model allow us to examine whether the parameter values differed between groups and provided the estimates of the model parameters for each group.

4) Cross Validation of the Statistical Model Across Groups: As shown below, we did not find any group differences in the model parameters, with the exception of the intercept. This indicates that the only difference in the associations between groups was an overall level of depressive mood, which suggests that it is possible to estimate mood changes around an overall mean level in one group (e.g., depressive scores in depression group)

TABLE II
MEAN LEVELS OF MOMENTARY SYMPTOMS AND LOCAL STATISTICS OF LOCOMOTOR ACTIVITY

	Mean (SE)		
	MDD	Healthy	*p* value
Momentary symptoms			
Depressive mood	58.95 (2.73)	41.64 (1.59)	<0.001
Anxious mood	58.68 (4.15)	39.03 (2.41)	<0.001
Fatigue	56.59 (5.04)	31.12 (2.90)	<0.001
Local statistics of locomotor activity			
Mean	111.59 (5.08)	132.61 (3.08)	<0.001
Skewness	0.47 (0.07)	0.11 (0.04)	<0.001

SE: Standard error. MDD: Major depressive disorder. All local statistics of locomotor activity were evaluated from the data collected within 60 min centered around EMA recordings.

TABLE III
PARAMETER VALUES OF THE IDENTIFIED STATISTICAL MODEL FOR DEPRESSIVE MOOD AND THEIR GROUP DIFFERENCES

	Coefficient (SE)	*F* value	*p* value
Identified model			
Intercept (γ_{00})	50.11 (2.45)		<0.001
Coefficient of the local mean (γ_{10})	-0.03 (0.01)	$F_{1,1653} = 7.01$	0.008
Coefficient of the local skewness (γ_{20})	1.82 (0.70)	$F_{1,1653} = 6.81$	0.009
Coefficient of the local mean × local skewness (γ_{30})	-0.01 (0.01)	$F_{1,1653} = 4.70$	0.030
Group difference of model parameters			
Intercept (γ_{00})		$F_{1,55} = 18.18$	<0.001
MDD	64.41 (3.70)		<0.001
Healthy	44.41 (2.71)		<0.001
Coefficient of the local mean (γ_{10})		$F_{1,1650} = 1.02$	0.312
MDD	-0.05 (0.02)		0.013
Healthy	-0.03 (0.02)		0.133
Coefficient of the local skewness (γ_{20})		$F_{1,1650} = 0.23$	0.631
MDD	1.79 (0.79)		0.023
Healthy	0.91 (1.67)		0.587
Coefficient of the local mean × local skewness (γ_{30})		$F_{1,1650} = 0.18$	0.671
MDD	-0.01 (0.01)		0.079
Healthy	-0.01 (0.01)		0.585

SE: standard error. MDD: major depressive disorder. The statistical model is as follows: Depressive mood $\mathrm{scores}_{ij} = \gamma_{00} + \gamma_{10}(\mathrm{Mean}_{ij}) + \gamma_{20}(\mathrm{Skewness}_{ij}) + \gamma_{30}(\mathrm{Mean}_{ij} \times \mathrm{Skewness}_{ij}) + \zeta_{0i} + \zeta_{1i}(\mathrm{Mean}_{ij}) + \varepsilon_{ij}$. For estimating the group difference of model parameters, a categorical variable representing the type of group (i.e., MDD and Healthy) was added into the intercept and slopes of the model above.

using the model derived from the other group (e.g., the model of healthy group) and vice versa, once the adjustment for the intercept is properly conducted. The cross validity of the derived models was particularly examined as follows. We estimated the depressive mood scores of healthy subjects using the model with the parameter values for the MDD group provided by the analysis described above. To estimate the scores, we substituted the local statistics of locomotor activity of a healthy subject into the model of the MDD group, in which the local statistics were evaluated from the data with a length of 60 min centered around EMA recordings. All random terms in the model were set to zero because of their definition. In addition, we estimated the depressive mood scores of patients with MDD using the model of the healthy group. The cross validity was evaluated by examining the correlation coefficient between estimated and self-reported depressive mood scores via a two-level mixed MANOVA model using depressive mood scores as the dependent variable and the type of score (i.e., estimated or self-reported score) as the predictor [25].

III. RESULTS

A. Recording Profiles

We obtained 1921 [137.2 (mean) $\pm$ 63.6 (SD) per person] EMA recordings from patients with MDD and 1781 recordings (41.4 ± 5.0) from healthy subjects. If simultaneous locomotor activity data were not acquired properly because of trouble with the device, we excluded the data from the analysis. Also, the periods during which the subjects were sleeping or had taken off the device due to, e.g., taking a shower/bath were excluded from the analysis. Finally, we obtained 767 (54.8 ± 23.3) sets of simultaneous recordings of EMA and locomotor activity data from patients with MDD and 946 (22.0 ± 4.7) such recordings from healthy subjects.

Table II summarizes the mean levels of subjective symptoms and the local statistics of locomotor activity used for the analysis. The mean levels of all symptoms in patients with MDD were significantly higher than those observed in healthy subjects ($p < 0.001$). The mean activity levels of patients with MDD were significantly lower than those of healthy subjects ($p < 0.001$), whereas the values of skewness were significantly higher in the patients than in controls ($p < 0.001$). These differences in the local statistics of locomotor activity indicate the increased intermittency of behavior dynamics, which is phenomenologically compatible with our recent findings of alterations of scale-invariant statistics in patients with MDD derived from long-term (>7 days) locomotor activity data [17]. This indicates that the increased intermittency observed in patients can also be captured by alterations in the local statistics, particularly the combination of decreased mean activity levels and higher positive values of skewness.

B. Identification of the Statistical Model for Depressive Mood

The statistical model identified from the combined dataset from both groups was a linear combination of the local mean, skewness, and their interaction as predictors, in which the local mean and intercept had a random effect: Depressive mood $\mathrm{scores}_{ij} = \gamma_{00} + \gamma_{10}(\mathrm{Mean}_{ij}) + \gamma_{20}(\mathrm{Skewness}_{ij}) + \gamma_{30}(\mathrm{Mean}_{ij} \times \mathrm{Skewness}_{ij}) + \zeta_{0i} + \zeta_{1i}(\mathrm{Mean}_{ij}) + \varepsilon_{ij}$. The coefficients of all the predictors were significant (see Table III), with a positive value ($\gamma_{20} = 1.82 \pm 0.70, p = 0.009$) for skewness and negative values for both the mean ($\gamma_{10} = -0.03 \pm 0.01, p = 0.008$) and interaction ($\gamma_{30} = -0.01 \pm 0.01, p = 0.030$). These results indicate the presence of a significant association between the increased intermittency of locomotor activity and worsening of the self-reported depressive mood.

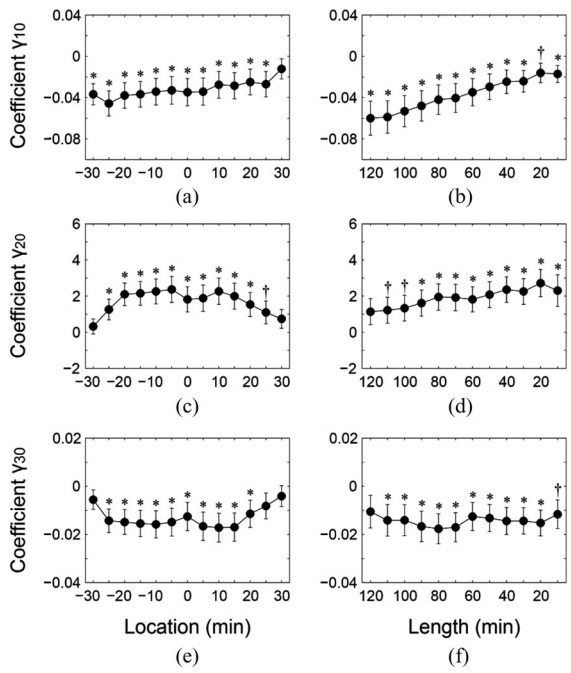

Fig. 2. Dependence of model coefficients on different locations and data lengths. Coefficient of the predictors: (a) Mean (γ_{10}), (c) skewness (γ_{20}), and (e) mean $\times$ skewness (γ_{30}) of the model identified as a function of the location. In these panels, the data length was fixed at 60 min. The same is shown in panels (b), (d), and (f), with the exception of the dependence on the data length. Here, the center of the data used for the derivation of the statistics was fixed at the timing of the EMA recording. Error bars indicate the standard error of the mean. The asterisks and daggers indicate that the model coefficients are significantly different from zero at $p < 0.05$ and 0.10, respectively.

The negative coefficient of interaction term possibly reflects situations in which the depressive mood becomes worse with both lower activity levels and positively larger skewness; thus, more frequent episodes of bursts are observed.

We demonstrated the robustness of the model identified against the choices of the data length and temporal location that were used to calculate the local statistics of locomotor activity. Fig. 2 shows the dependence of the coefficients of three predictors on the different values of choices. All coefficients were consistently significant over a broad range of location [see Fig. 2(a), (c), and (e)] and data length [see Fig. 2(b), (d), and (f)] values, which was indicative of the robustness of the model identified.

C. Group Differences in the Associations Between Depressive Mood and Locomotor Activity

There were no significant differences in the coefficient of all predictors, with the exception of the model intercept (see Table III). This indicates that identical relationships between changes in mood and behavior exist across patients with MDD and healthy subjects, although the patients had higher levels of overall depressive mood scores, as represented by the higher intercept values.

Table III summarizes the estimates of model coefficients for both groups. All the coefficients in patients with MDD were significant, with the exception of the interaction term with a significant positive value ($\gamma_{20} = 1.79 \pm 0.79, p = 0.023$) for skewness and negative values for both the mean ($\gamma_{10} = -0.05 \pm 0.02, p = 0.013$) and their interaction ($\gamma_{30} = -0.01 \pm 0.01, p = 0.079$). In contrast, none of the coefficients estimated in healthy subjects were significant ($\gamma_{20} = 0.91 \pm 1.67, p = 0.587$ for skewness; $\gamma_{10} = -0.03 \pm 0.02, p = 0.133$ for the mean; and $\gamma_{30} = -0.01 \pm 0.01, p = 0.585$ for the interaction), whereas the signs of all coefficients were consistent with those estimated for the MDD group. The difference in the significance of the model parameters between groups may have been caused by the difference in within-individual sample sizes (on average: 54.8/person for the MDD group and 22.0/person for the healthy group). However, even these parameters for the healthy group fit well in the cross-validation study which are shown below.

D. Cross Validation of the Statistical Model Across Groups

The correlation between self-reported depressive mood in patients and estimated scores based on the model for the healthy group was significant (correlation coefficient $r = 0.21; p < 0.001$). Regarding the depressive mood scores of healthy subjects, the correlation coefficient was also significant ($r = 0.10, p < 0.001$). These results indicate the cross validity of the models identified or the presence of shared psychobehavioral correlates across groups.

IV. Discussion

In this study, we examined psychobehavioral correlates between momentary depressive mood and behavioral dynamics in patients with MDD. We particularly evaluated the within-individual associations between changes in momentary self-reported depressive mood scores and the local statistics of locomotor activity simultaneously measured. While most studies have investigated the between-individual associations between locomotor activity and subjective symptoms [36], this study examined the associations on a within-individual basis. In addition, as prior studies suggested [36], [37], these associations were revealed by multimodal interactive assessment of repeatedly measured momentary depressive mood by ED and objectively obtained locomotor activity. We believe that this ensures enhanced understating of psychobehavioral correlates in MDD.

The statistical model that described the associations showed increased intermittency of behavioral dynamics with worsening of depressive mood. This result suggests that it is possible to estimate momentary depressive mood from the objective measures of locomotor activity; thus, leading to continuous monitoring of the pathogenic processes and pathological changes of MDD. Furthermore, we confirmed the cross validity of the model describing within-individual associations across healthy subjects and patients with MDD. The existence of shared psychobehavioral correlates between groups implies that changes in momentary depressive mood in healthy individuals, like those recorded for clinically depressed patients, can also be estimated from locomotor activity data. However, we also found the group difference in the overall level of depressive mood score (i.e., the intercept) suggesting that the model for healthy individuals

cannot be simply used to predict depressive mood levels of the patients. Such discontinuity in psychobehavioral relations between healthy subjects and the patients might have implications for the pathogenic processes; hence, the prevention and/or early detection of MDD. Continuous monitoring of psychobehavioral dynamics for the high-risk subjects developing MDD (e.g., subjects who show a high level of depressive mood) would be expected to provide more detailed pathogenic processes in the future research.

The intermittent and bursty nature of human behavioral dynamics is now receiving attention in various scientific fields [38]–[42]. Recently, we found the increased intermittency of locomotor activity in patients suffering from MDD [17] and schizophrenia [43], which was indicative of more frequent episodes of slowing down or cessation of movement, while having occasional bursts in these patients compared with healthy subjects [e.g., days 3–4 of Fig. 1(b) compared with Fig. 1(a)]. Furthermore, we proposed a possible theoretical model for intermittent behavioral dynamics and its alterations based on a priority stochastic queuing theory [44]. According to this model, the increased intermittency observed in patients with MDD can be explained by a strategic change in decision making to initiate actions with preferential selectivity to demands (cues) with higher priority. Patients with MDD tend to react only to higher demands and/or stimuli (generating occasional activity bursts) and stay quiet for most of the time (resulting in reduced activity). The results of this study further suggest that such a strategic change can be associated with alterations in momentary depressive mood, leading to increased local intermittency in locomotor dynamics.

The advancement of information and communication technologies has led to the recent rigorous development of healthcare monitoring systems that often combine mobile technologies [45]–[47] and are expected to play a considerable role in early detection, management, and treatment of psychiatric disorders, including MDD, bipolar disorder, and schizophrenia [46], [47]. To successfully establish such systems, many essential elements have been under study. For example, the concept of ecological momentary interventions (EMIs), in which real-time interventions are delivered to individuals during their everyday lives in natural settings, is a core elemental technology that is used for novel treatments of these diseases [48]. In contrast, the sign-contingent EMA, which is an assessment that is triggered by a warning "sign" related to the disorders, is considered useful for detecting early signs of psychiatric disorders and their pathological transitions [35], [49]. However, the development of objective, reliable, and, more importantly, real-time biobehavioral markers for psychiatric disorders is necessary to establish these important elements; thus, the demand for such markers has grown recently. In this context, this study has a great potential to contribute to the establishment of healthcare systems by providing an objective and real-time biobehavioral marker, i.e., a statistical model for depressive mood based on behavioral dynamics. In addition, our findings serve as useful models for continuous monitoring and estimation of depressive mood, as well as fundamental techniques for the realization of EMIs and sign-contingent EMA.

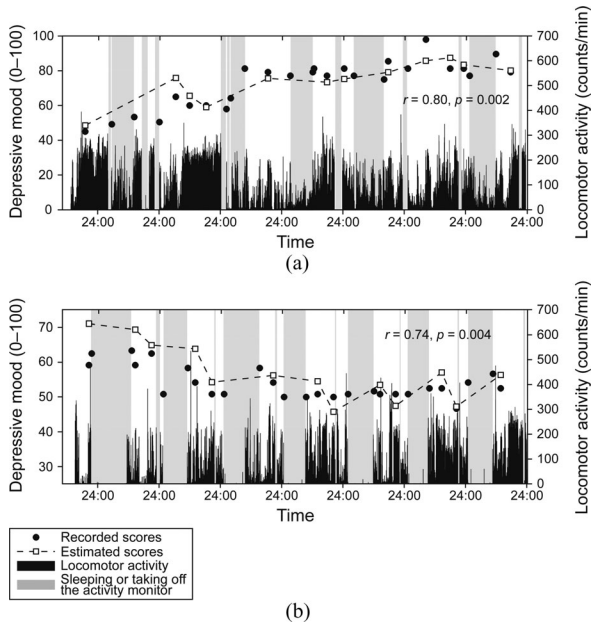

Fig. 3. Estimation of depressive mood scores using personalized models. Open squares indicate the estimates of depressive mood scores (*y*-axis on the left side) by substituting the local statistics of locomotor activity (within 60 min centered around the EMA recording) into the statistical model with personalized parameter values. The personalized parameter values for subject no. 12 (upper) were: $\gamma_{00} = 83.78$, $\gamma_{10} = -0.08$, $\gamma_{20} = 1.17$, and $\gamma_{30} = -0.01$, whereas those for subject no. 6 (lower) were: $\gamma_{00} = 70.38$, $\gamma_{10} = -0.15$, $\gamma_{20} = 4.08$, and $\gamma_{30} = -0.06$. The correlation coefficients *r* and their *p* values between the estimated and self-reported scores were 0.80 and 0.74, respectively. Note that the estimation of depressive mood was only made for periods in which the subjects were awake and wearing the device (a) Patient No. 12 (b) Patient No. 6.

One potential limitation of this study was that the correlation coefficients obtained in the cross validation of the identified model were small, although the correlations themselves were significant. These low correlation values may be because of wide individual differences, such as lifestyle, pathological conditions, and effects of antidepressant medication. However, these individual effects may be minimized by optimization methods, such as support vector machine [50] or neural network approaches [51]. For example, the personalization of the model structure and its parameters using the data of the first few weeks could minimize the individual effects and improve the ability to estimate depressive mood scores. In fact, we could improve the estimation of the depressive mood scores merely by personalizing the model parameters using simple linear models employed in this study. Fig. 3 shows typical cases in which the estimation was highly improved by this type of personalization. The parameters of the model derived in this study were optimized individually using data collected at one week in the early part of the measurement. Subsequently, the depressive scores in another week in the later part of this study were estimated using personalized parameters. In these patients, the correlation coefficients between self-reported and estimated depressive mood scores were considerably higher [$r = 0.80$ ($p = 0.002$) for Fig. 3(a) and $r = 0.74$ ($p = 0.004$) for Fig. 3(b)] than those calculated for the overall cross validation. Although we were unable to perform this optimization procedure for the data from all

patients because this requires relatively long-term measurements (>2 weeks), we confirmed considerable improvements in the estimation in six patients who had this condition with correlation coefficients ranging from 0.48 to 0.80. Other sophisticated optimization methods would probably highly improve the estimation.

In addition, the inconsistency of the EMA protocols between patients with MDD and healthy subjects could be a limitation of this study. Also, diagnostic interviews such as MINI have not been performed for healthy subjects in this study. Therefore, careful consideration is needed when we consider group differences on the findings. Furthermore, there can be a systematic bias that the data just before/after sleeping or taking a shower can be easily excluded from the analysis; this should be considered when we interpret the findings. The other weaknesses of this study included the effects of medications on behavioral dynamics and the small sample size. Thus, the generalization of our findings will require a large population study using drug-free patients. Another issue that should be addressed is the ceiling effect. Although patients with MDD showed a level of variability in depressive mood scores that was comparable with that of healthy subjects, four patients occasionally reported maximum scores during the study period. Because of the low rate (2.76%) of such data points, we believe that the ceiling effect was limited in our study; however, there is a possibility that the associations observed were slightly distorted by such an effect.

V. Conclusion

We demonstrated the presence of associations between momentary depressive mood and behavior dynamics, and showed their cross validity across patients with MDD and healthy subjects. **The results suggest that it may be possible to objectively estimate a momentary depressive mood based on pattern of physical activity**; thus, leading to continuous monitoring of the pathogenic processes and pathological states of MDD.

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