Dynamic Patterns in Mood Among Newly Diagnosed Patients With Major Depressive Episode or Panic Disorder and Normal Controls

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Objective: The purpose of this pilot study was to compare the dynamic patterns of hourly mood variation among newly diagnosed primary care patients with major depressive disorder or panic disorder with patterns in patients with neither disorder.

Method: Five adult patients with major depressive episode, 5 with panic disorder, and 5 with neither disorder were asked to complete hourly self-assessments of anxiety and depression (using 100-mm visual analog scales) for each hour they were awake during a 30-day period. Time series were analyzed using ARIMA (autoregression, integration, moving average) modeling (to assess periodicity), Lyapunov exponents (to assess sensitivity to initial conditions indicative of chaotic patterns), and correlation dimension saturation (to assess whether an attractor is limiting change). The study was conducted from March to June 2003.

Results: Controls displayed circadian rhythms with underlying chaotic variability. Depressed patients did not display circadian rhythm, but did show chaotic dynamics. Panic disorder patients showed circadian rhythms, but 2 of the 4 patients completing the self-assessments displayed nonchaotic underlying patterns.

Conclusions: Patients with major depressive disorder or panic disorder may differ from controls and from each other in their patterns of mood variability. There is a need for more research on the dynamics of mood among patients with mental disorders.

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There is evidence that dynamic patterns of changes in symptoms and behavior over time are important in mental illness. Observations that light therapy can affect circadian rhythms among depressed patients suggest that mood variation over time may be important clinically among patients with mental illness.[1,2]

Complexity of symptoms or behaviors in an individual is often characterized by the dynamics of the individual's longitudinal patterns. While periodic/linear temporal patterns are predictable in both trajectory and pattern, chaotic patterns are predictable in pattern only. Random dynamics are predictable in neither trajectory nor pattern. Such random dynamics display power laws (frequency distributions often seen in complex interacting living systems), in which one variable varies inversely with the exponential change of another, resulting in dynamic patterns that vary in similar ways regardless of the time interval.

Not only is nonlinear dynamics, in which the input at one moment is not proportional to the output at the next moment, relevant to posttraumatic stress disorder, schizophrenia, addiction, depression, and phobic and suicidal behavior,[3] but it may be instrumental in addictive, self-destructive, and dysfunctional behavior.[4] In fact, outpatient recovery patterns among psychiatric inpatients exhibit several nonlinear features.[5] Power laws can explain detoxification patterns among alcoholics[6] and social interaction patterns on psychiatric wards.[7] Dynamics assessment has also been applied to mood variability in specific disorders. Just as phototherapy has been used to correct circadian rhythm problems in depressed patients, attempts to control problematic thoughts and emotions among patients with generalized anxiety disorder and personality disorders may produce nonlinear dynamics patterns of daily mood variation.[8] Also, mood dynamics is important in bipolar disease; random dynamics in controls differs from the chaotic dynamics among bipolar outpatients and rapid cycling among bipolar inpatients.[9,10] This pattern of randomness-to-periodicity in controls-to-inpatients supports the idea that variability reflects health and suggests that the more severe the illness, the more regular the dynamics. Although counterintuitive, the idea of equating health with variability has been noted in heart rate, brain

wave activity,[11] gastrointestinal motility,[12] and response to medication.[13,14] In fact, aging is associated with loss of variability and complexity.[15]

Nonlinearity of mood variation may be particularly important in primary care settings. The fact that depressed patients in primary care settings are less symptomatic (and less severely ill) than those in psychiatric settings[16] would suggest that they may display more nonlinearity. Such patients should be less predictable in their response to therapy.[17] This may explain the high intersite variability in antidepressant response and placebo effect.[18]

Although previous studies[8–10] have involved small samples with imprecise data, their findings suggest that nonlinear patterns of mood variability may be common among primary care patients. Because there is a lack of understanding of how mood varies in different disorders, an exploratory study was conducted that might suggest possible differences in dynamics across disorders and approaches to their study. The purpose of this pilot study was to describe the dynamic patterns of hourly mood variation among newly diagnosed primary care patients with major depressive disorder or panic disorder with patterns in patients with neither disorder.

METHOD

Sample

The sample was obtained by referral from 2 primary care clinics at the University Health Center-Downtown in San Antonio, Tex.—the Family Health Center and the Acute Care Clinic. English-speaking adult (age ≥ 18 years old) patients were referred for enrollment by their physicians if they had newly diagnosed panic disorder or major depressive disorder without other mental illness, or if they had neither diagnosis. Once informed consent was obtained, patients referred for enrollment completed the panic disorder and major depressive episode sections of the Structured Clinical Interview for DSM-IV.[19] Patients meeting criteria for either current panic disorder or major depressive disorder (but not both disorders) were asked to participate in the study. In addition, patients with no history of either disorder were asked to participate as a control group. Five subjects with panic disorder, 5 subjects with major depressive disorder, and 5 control subjects were enrolled. This study was reviewed and approved by the institutional review board. The study was conducted from March to June 2003.

Procedure and Measurement

Once enrolled, each subject provided demographic information. Their medical records were reviewed to ensure that they were not taking psychotropic medication prior to the visit and to document their active diagnoses and any treatments received for newly diagnosed panic disorder or major depressive disorder.

In addition, subjects were asked to complete a mood diary for the next 30 days. Each hour on the hour while awake, subjects were asked to indicate their levels of anxiety (0 = "very relaxed," 100 = "very nervous") and depression (0 = "very happy," 100 = "very sad") using 100-mm visual analog scales. Visual analog scales have been extensively used in studies of mood in outpatients[20] because they have established validity and reliability and are sensitive to change over time.[21] A wristwatch with an hourly chime was given to subjects to remind them to complete the ratings each hour. The research assistant contacted each subject weekly to answer questions concerning the diary and encourage ongoing participation. Subjects were compensated for their participation. In each group, 4 out of 5 subjects completed the diary.

Dynamics Analysis

Dynamical patterns depend upon 2 principal factors. First, are the data sensitive to initial conditions; does a small change initially send the system on a new trajectory, drastically changing the system's subsequent performance? Second, is an attractor present; is something limiting the range of possible behaviors of a system and preventing random activity? In this study, dynamics were assessed through analysis of time series data. Primary analysis consisted of 3 assessments. Time series analysis was performed to look for an ARIMA (autoregression, integration, moving average) model that would fit the data. Nonstationary time series that either progressively increase or progressively decrease (defined by the first order autocorrelation ≥ 0.9) were first differenced to yield stationary results. Because autocorrelation analysis suggested seasonality (in this case, a circadian pattern) in most subjects, all data were seasonally adjusted and dynamics analysis was performed using the residuals. Although (0,0,0) ARIMA models (those not needing adjustment to account for the time series) suggest randomness, all other models suggest periodic dynamics. Sensitivity to initial conditions was assessed by the Lyapunov exponent, which measures the speed with which adjacent points separate over time. If the exponent is positive, then trajectories diverge and the system is sensitive to initial conditions and is chaotic or random. If the exponent is negative, then the trajectories converge and the system is usually periodic, although random dynamics can occasionally yield a negative exponent.[22] To determine the existence of an attractor (something limiting the range of possible behaviors), the Chaos Data Analyzer software[23] is used to calculate the correlation dimension of the system and embedding dimension. The correlation dimension should stabilize if the system has an attractor (chaotic or periodic). The embedding dimension is the spatial dimension of the system at which the correlation dimension of the attractor no longer increases.

Table 1. Dynamic Patterns Among Subjects[a]

Subject	Mood Level[b] Mean (SD)	Minimum/ Maximum	ARIMA	Lyapunov	Correlation Dimension	Entropy	Surrogate Testing	Interpretation
Depression								
D2	80.60 (12.33)	24/98	Infradian	.271	5.09	.508	< .05	Chaotic
D3	76.40 (14.59)	41/98	Differenced	.203	3.67	.796	< .05	Chaotic
D5	67.30 (19.52)	2/98	…	.353	3.31	.320	< .05	Chaotic
C1	24.60 (11.09)	2/63	Circadian	.218	4.90	.492	< .05	Chaotic
C2	37.80 (12.88)	10/81	Differenced	.133	1.11	.697	< .05	Chaotic
C3	29.70 (5.00)	19/48	Circadian	.277	4.75	.573	.10	Chaotic
C4	11.90 (7.42)	2/70	Circadian	.058	4.12	.514	< .05	Chaotic
Anxiety								
C1	30.10 (11.83)	3/61	Circadian	.199	5.00	.527	< .05	Chaotic
C2	37.10 (13.64)	7/71	Differenced	.166	1.35	.661	< .05	Chaotic
C3	32.90 (4.90)	12/48	Circadian	.253	5.32	.532	.60	Uncertain
C4	11.30 (5.83)	2/53	Circadian	.088	2.98	.566	< .05	Chaotic
P1	46.00 (12.96)	16/84	Circadian	.261	4.91	.313	< .05	Chaotic
P2	67.10 (15.68)	22/100	Circadian	.278	4.16	.500	< .05	Chaotic
P3	71.60 (27.40)	0/100	…	Inconsistent	…	.258	…	Random
P4	22.20 (11.92)	5/75	Circadian	.253	4.45	.516	…	Periodic

[a]Subjects with missing/incomplete data = D1, D4, C5, P5.
[b]Measured using a 100-mm visual analog scale; for depressed patients and controls, level of depression was measured from 0 = "very happy" to 100 = "very sad"; for panic disorder patients and controls, anxiety was measured from 0 = "very relaxed" to 100 = "very nervous."
Abbreviations: ARIMA = autoregression, integration, moving average; C = control patient; D = depressed patient; P = panic disorder patient.
Symbol: … = not applicable.

Based upon these 3 assessments, a provisional determination of dynamics can be made. However, the above results are only suggestive of the particular dynamic pattern. For example, the Lyapunov exponent can be negative in a chaotic or random[22,24] system under certain circumstances. These techniques were originally designed for analyzing long time series (N > 1000) and thus should be interpreted with caution when smaller data sets are used.

To confirm the provisional assessment of chaotic dynamics, surrogate testing was performed. In surrogate testing, time series data are shuffled using phase randomization, which produces a time series with similar linear dynamics but different nonlinear dynamics.[25] For each analysis, the randomization was repeated 20 times and the resulting correlation dimension was compared to the correlation dimension of the original data. Because the linear dynamics are maintained, we would expect that several of the surrogate data sets would have correlation dimensions less than or equal to those of the original data, if those data come from a periodic system. However, if the original data came from a nonlinear (chaotic) system, then few of the surrogate data sets would have correlation dimensions less than or equal to those of the original data. The proportion of surrogate data sets with correlation dimensions less than or equal to that of the original data gives a measure of statistical significance. For a pattern to be assessed as "chaotic" in this study, surrogate testing had to yield a $p \leq .05$.

In addition to the assessment of the specific dynamic pattern in each subject, we computed the entropy (sum of the positive Lyapunov exponents in base e) of the seasonally adjusted residuals as a measure of overall nonlinearity.[26] The higher the entropy value, the more nonlinear is the time series. Entropy does not correlate with either mean or standard deviation of mood levels in normal controls.[20] Intergroup differences in entropy were sought using the Wilcoxon signed rank test.

RESULTS

Of the 15 patients enrolled, 8 were female, 10 were Hispanic, and 12 were over 40 years old. Only 6 patients had a high school education, and 10 reported a household income under $30,000. Three depressed patients received antidepressant medication, but only 1 patient with panic disorder received antipanic medication. Based upon the self-reported wake and sleep times, 11 of 12 subjects completing the mood diary had missing data rates of 0% to 2.4%. One subject (D4) failed to document 40.1% of ratings and was not included in the dynamics analysis.

Table 1 presents the minimum, maximum, and mean and temporal variability of symptom levels for each subject. Although patients with major depressive episode and panic disorder reported similar mean and maximum symptom levels, all 3 groups had similar minimum levels.

Table 1 also presents the results of the dynamics analyses. From the ARIMA analysis, circadian patterns were seen in most controls and panic disorder subjects. Lyapunov exponents were generally positive and correlation dimensions usually saturated, suggesting chaotic dynamics of mood variation in seasonally adjusted residuals. In only 1 subject (C3) did surrogate testing not sup-

port the chaotic dynamics of mood variation suggested. Controls generally exhibited circadian patterns whose residuals generally suggested chaotic dynamics. As groups, depressed subjects differed from controls in their lack of circadian patterns of mood variation. Panic disorder subjects differed from controls in that dynamics in 2 subjects was not suggestive of chaos; 1 subject exhibited periodic dynamics and 1 exhibited randomness in mood variation over time. Controls displayed significantly higher entropies than did panic subjects (Wilcoxon signed rank $Z = -2.309$, $p = .029$), confirming their more nonlinear patterns.

DISCUSSION

We used this exploratory longitudinal study to gain a foothold on understanding the dynamics of mood variability among 3 groups of primary care patients. This pilot study found that controls generally exhibited circadian changes in both anxiety and depression levels, with residuals displaying chaotic dynamics in mood variation. Patients with depression displayed the chaotic dynamics but no circadian variability. Patients with panic disorder showed circadian patterns, but only 2 of 4 exhibited chaotic dynamics.

Healthy patients may experience and report maximum and minimum mood levels that reflect their circadian pattern with interspersed mood fluctuations in response to intermittent stressors. Depressed patients, without that circadian rhythm, may only experience the fluctuations without a reliable daily maximum and minimum mood level. Patients with panic disorder may, however, report the reliable daily extremes without the irregular fluctuations in response to stressors.

If this pilot study truly reflects general mood variability patterns across these disorders, then it opens the possibility that major depressive disorder and panic disorder may differ from normal controls and each other in their dynamic patterns and/or circadian variability, and that future research may suggest clinically important applications. First, healthy dynamics of mood variation may be characterized by a circadian pattern with underlying chaos. Second, in depression, the circadian pattern of mood variation may be lost, while in panic disorder, the underlying chaos may be lost. In general, among patients with depression or panic disorder, the Lyapunov exponent increased, suggesting more sensitivity to stressors, and the correlation dimension decreased over time, suggesting stronger attractors limiting the range of possible moods, possibly suggesting a shift toward chaos. Third, monitoring dynamics in mood may be useful in assessing early response to treatment and relapse. Fourth, the different dynamic patterns observed raise the question whether dynamics analysis may have treatment implications (patients with certain dynamic patterns may respond differently to certain medications after controlling for confounding factors, such as patients' characteristics [e.g., periodic dynamics should be more responsive than chaotic or random dynamics]). Finally, the majority of research has focused on dynamics of heart rate rather than mood. There is enough evidence to call for more research on the dynamics of mood in patients with mental disorders.

This study has obvious limitations. First, the sample size is small for time series analysis. However, time series analyses have been conducted on data sets with as few as 100 data points.[24] Studies of corporate innovations used 50, 74, and 102 data points.[22] In addition, patterns of mood change in patients with bipolar disorder[9] and migraines[27] were conducted using as few as 227 and 280 data points, respectively. Second, reliance on referral of subjects from their physicians rather than a random sample may have resulted in selection bias, potentially favoring referral of more severely ill patients with potentially different (and more periodic) dynamics.

Another limitation was that nonrespondents and the one subject whose data were not used due to the amount of missing values may have displayed different dynamics. For example, the depressed subject not used in the dynamics analysis was the only depressed subject not started on antidepressant treatment initially, which may in turn be related to the dynamics observed (either more severe symptoms or more extreme mood swings). Although antidepressants typically require weeks of therapy before significantly impacting mood, the inclusion of subjects taking antidepressants could have affected the outcome, resulting in dynamics characteristic of controls; however, few week 1–week 4 differences in entropy or standard deviation in depressed mood among the depressed patients were found. The use of visual analog scales could be problematic. Although shown to be reliable and valid, visual analog scales reduce mood to a single item and are therefore sensitive to minor effects; measurement error decreases the likelihood of finding evidence of chaotic dynamics.[28,29] In addition, because measurements were taken only while subjects were awake, the time series may be discontinuous and dynamics analysis problematic. Also, reflecting hourly on one's own mood may in itself represent an intervention that could affect subsequent dynamics; however, studies done on hourly assessment of pain level did not suggest that it affected subsequent assessments.[30] When seasonally adjusted overnight differences were compared to first morning and penultimate changes, significant differences were generally found, except among depressed patients. Because measurements were taken only when subjects were awake, further investigation on the effects of discontinuity in the time series is needed to confirm our dynamics analysis. Even though subjects were contacted weekly, it is possible that diaries were not completed hourly but rather completed only at

the end of the study and thus do not accurately reflect the dynamics as they occurred; such "cheating" is likely to miss chaotic dynamics. Finally, the demographics and comorbidities among subjects may limit this study's generalizability.

CONCLUSION

In conclusion, this initial pilot study suggested that levels of anxiety and depression varied with a circadian pattern and underlying chaos among controls. Depression patients tended to display chaotic dynamics of mood variation but without circadian patterns. Panic disorder patients tended to exhibit circadian patterns but sometimes without underlying chaos. These results demonstrate the need for more research on the dynamics of mood among patients with mental disorders to determine whether this pilot study truly reflects general mood variability patterns.

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