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A Whole New World: Complexity Theory and Mood Variability in Mental Disorders

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At first glance, the article by Katerndahl and colleagues on dynamic patterns of mood variation seems to be from an alternate universe. *What?* Check mood symptoms *hourly*? What does this have to do with anything clinical? *Of course* moods change during a day—that's why they're called "moods." What can they possibly be thinking?

But look again, a bit more closely this time. What Katerndahl and colleagues have produced is in many ways a groundbreaking effort.

Consider what we know about mood disorders. We cannot see them. We cannot identify them by an unambiguous laboratory test. Our diagnoses are based upon clusters of reported symptoms that expert clinicians believe reflect a cohesive package of internal emotional dysfunction. We call depression a "brain disease," but even in the fMRI era we cannot identify the area of the brain where the "disease" occurs. Instead, we rely on patients' recollections of their predominant mood states over a 2-week period. But can we be sure that *predominant* means the same thing to our patients as to our classifiers and diagnosers? Which mood do patients recall and report as "predominant"? Their most intense mood? The mood that has been present most of the time? The one perceived as most dysfunctional? How can we be sure patients respond to the items on our diagnostic instruments in the same way we frame them?

I conducted a brief experiment in my office a few weeks ago. I gave each of my depressed patients a paper copy of the Patient Health Questionnaire-9 (PHQ-9) instrument, and after they completed it I asked them to explain what they meant by their answer to each item. All had seen and completed this instrument previously. I expected that an occasional patient might ignore the 2-week instruction on the form and respond based upon their current mood, but I found, to my surprise, that almost half were basing their responses on current mood. One said, "It's a good thing my appointment was today . . . if you had given me this yesterday, my score would have been much worse."

This anecdote is not intended to cast doubt on the reliability or validity of the PHQ-9; both have been confirmed in clinical trials.[1–4] I simply use it to illustrate how poorly our current diagnostic methodology captures the complexity of the clinical condition we call depressive disorder. Everyone's moods vary. But we don't know how much they vary in a day—or an hour—or what might be different between individuals who clearly seem to have a "disorder" and those considered normal. What Katerndahl and colleagues have done is to ask exactly this basic question about mood variability and to try to answer it using tools that have shown promise in the study of other clinical conditions.

Their premise is that, in "normal" persons, mood states might vary over time in a dynamic pattern similar to that seen for heart rate. Heart rate variability in normal persons has been shown to have a complex, nonlinear pattern that follows some of the mathematical patterns of complexity. Since one of the features of a diseased heart is its loss of dynamic variability, is it possible that one of the features of a diseased brain is also loss of dynamic variability in mood symptoms?

It is an intriguing question, and Katerndahl and colleagues explore it using an innovative method that borrows heavily from complexity theory and its mathematical toolbox. There is not a lot of prior work to guide them; this is by no means a mature science. The team assessed patterns of mood variation in 15 patients—5 patients with major depressive disorder and 5 with panic disorder (confirmed by a standard structured clinical interview, without comorbid disorders) and 5 controls. They began with a very simple measure for each of their key variables, hourly assessment while awake of levels of depression and anxiety over a 30-day recording period using a 0-to-100 visual analog scale. Numerical scores for each rating over the full 30-day period became the input variable in a time-series analysis that assessed for dynamic patterns

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in the data. Following methods established in prior work, they looked for the presence of randomness, periodic dynamics, or chaotic dynamics and the presence or absence of an attractor (in chaos theory, an agent limiting the range of possible behaviors).

While the specific steps in analysis are difficult to fully understand (and review), the results of the analysis are described in clear terms. Four of 5 normal controls displayed a circadian mood pattern with chaotic dynamics. Depressed subjects did not show a circadian pattern of mood variation. Panic disorder subjects had variable patterns of mood dynamics but generally did not match the combination of circadian pattern, chaos, and level of nonlinearity seen in controls. Taken together, these results suggested that healthy individuals (those without a "disorder") might experience a normal circadian rhythm in mood with superimposed mood changes as the chaotic response to multiple social or biological stressors during a day, while either the circadian rhythm or the responsiveness to stressors is impaired in those with mood or anxiety disorders.

This pilot study contained significant limitations that make it important not to read too much into the results. There were only 5 subjects per group, and one of the groups did not display a consistent pattern. Four of the 5 depressed subjects were started on treatment with antidepressant medications during the observation period, which might have affected their perceived mood and altered their patterns of response. The use of a single "sad-happy" visual analog scale as proxy for depressed mood compresses a subjective, multidimensional construct (mood) into a single, perhaps pseudo-precise, number; this may not be comparable to the more objectively measured variables (heart rate, brain wave activity) assessed in other studies. The timing of mood assessment, hourly while awake, is arbitrary; we have no idea whether half-hour, every-other-hour, or some other interval would yield a different periodicity or dynamic pattern. It is not yet clear whether the specific ARIMA model used is the most appropriate method for assessing dynamic patterns, and as mentioned by Katerndahl, the number of data points per subject was quite small for this type of modeling. Finally, the discontinuous time series (missing sleeping hours) presents problems for time-series analytic methods. Most of these issues will need to be addressed in subsequent work, but there clearly seems to be enough evidence here to justify more research on dynamic patterns of mood in mental "disorders."

Is this the new phrenology? I don't think so. While it is too soon to know whether we are investigating something that is physiologically "real" and meaningfully related to disease, we have evidence that nonlinear dynamics is an important organizing principle in biological systems, and this study is an intriguing first step in developing our understanding of how "healthy" and "diseased" brains may respond to the internal and external environments in which they must function.

This line of research might be of particular importance as we refine our diagnostic classifications of mental and behavioral disorders. Returning to the example of my patient whose PHQ-9 score would classify him as "severely depressed" one day and "mildly depressed" the next, we clearly need to move beyond expert opinion and nosological diagnoses in deciding who has "brain disease."[5–8] We cannot maintain a system that defines mental disorder by criteria that are specific to the Western concept of mood and lead to several-fold differences in prevalence between Western and Eastern cultures.[9,10] Work is underway on DSM-V, and the World Health Organization has begun work on ICD-11; both groups are reassessing the validity of the basic diagnostic categories in our current classification structure.[11] If the approach introduced by Katerndahl and colleagues proves valid, we may be able to compare dynamic patterns of mood variability across diagnostic categories. We could learn which disorders exhibit similar patterns and may be related, which disorders exhibit different patterns and represent distinct conditions, and which conditions or "subthreshold" conditions show the same patterns as normal controls and may not be disorders at all.

We are now in a time when we can use functional brain imaging to identify patterns of brain activity in response to selected stimuli, and gene mapping to identify genetic features associated with specific mental disorders. If we can add dynamic pattern mapping to our new toolbox, our ability to identify and classify mental and behavioral disorders will be greatly enhanced. I look forward to the next steps in this line of research: exploring additional dimensions of mood, assessing other conditions, observing over longer periods of time, examining the impact of medication or other treatment on patterns. This is an exciting area for mental health research. Stay tuned.

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