The perils of being too stable: mood regulation in bipolar disorder

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Bipolar disorder or recurrent depression are traditionally conceptualized as series of discrete mood episodes interspersed with "normal" mood. But what does "normal" mean in this context? Mood that is completely stable? No mood changes at all? Does it mean that those adjustments (i.e., fluctuations) in mood that result from our continual interaction with the environment are problematic? It has long been recognized clinically that minor mood fluctuations are an intrinsic property of mood regulation both in healthy individuals and in euthymic patients with bipolar disorder, but methods for assessing mood variability are only now being developed and tested.

Major mood episodes have been the focus of both treatment and neurobiological studies, but there is growing recognition that interepisode intervals may provide important clues about the nature of mood disorders. Some authors view bipolar disorder as a condition of mood instability that persists into illness remission. Interepisode symptoms and functional impairment are relevant, as they are associated with risk of relapse and their absence is one of the best predictors of long-term lithium response. But less is known about the physiological underpinnings of mood regulation and mood changes during remission periods.

Mood regulation is a complex and poorly understood process. It can be conceived as a system allowing individuals to respond flexibly to changing and often unpredictable conditions. The study of mood disorders to date, however, has paid relatively little attention to this potentially key feature. From a dynamic point of view, the properties that enable this type of adaptability are considered to be complex. These properties include nonlinearity (systems do not respond proportionally to stimulation; i.e., small changes can have huge effects), lack of a single or characteristic scale (fractal- or tree-like organization) and emergent properties (properties that emerge from the whole, but were not present in the parts). Nonlinearity, however, does not imply a lack of underlying structure, as nonlinear systems have organized, discoverable principles. The challenge is that these principles are difficult to uncover using conventional analyses.

Mood patterns in individuals with bipolar disorder, although aperiodic, may be more organized than those of healthy individuals, which led to the description of mood in patients with bipolar disorder in terms of chaotic (nonlinear) dynamics.[1] Nonlinear methods offer new tools with which to quantify, model and attempt to predict the behaviour of complex systems.[2,3] Entropy is a type of nonlinear measure that reflects the amount of noise or disorganization in a system. A type of entropy, multiscale entropy, measures the complexity of a system and is often used in biology. Typically, lower entropy levels (corresponding to recognizable patterns in the data) may indicate impaired physiological regulations, as in cardiovascular[4] and metabolic diseases,[5] premenstrual dysphoric disorder[6] and bipolar disorder.[7]

Time-series analysis is another type of nonlinear method that is usually used to study a collection of observations made sequentially in time.[8] Mood also depends on time, as successive observations are not independent. Mood is continuously regulated by processes that reflect the behaviour of complex systems, with relatively simple mechanisms responsible for their functioning; the adaptability and variability of mood become impaired in patients with bipolar disorder.[7] This reduced flexibility, as indicative of illness, is not limited to mood processes: findings implicitly associating greater regularity with illness have been found in other clinical situations, such as in ventricular tachyarrhythmias or prior to a seizure.[9,10] If we can conceptualize mood regulation as a complex system, suitable mathematical models have the potential to provide insight into this entity.[11–13]

Mathematical models and their clinical correlates

Markov chains: Why do we need to recalibrate?

Markov chains have been used to model random processes. Their greatest strength is their capability to predict the immediate future based on what has happened in the recent past. The order of a Markov chain indicates the number of past

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states taken into consideration: events in a first-order chain are directly affected only by their immediate predecessors, events in a second-order chain are affected by two predecessors, and so on. Current data suggest that mood regulation might be a first-order process.[7,14] In other words, in healthy systems, we get a chance every 24 hours to "balance" or recalibrate the system, with sleep likely being one of the main contributors to this calibration.

Instead of conceptualizing mood as a relatively immutable state, it would be helpful to think of it as a continually adjusting system. In this sense, it would be advantageous to identify the particular variables that have an important role in calibrating this system. One of the most important ones is anxiety: rates of comorbidity between anxiety disorders and bipolar disorder are rather high,[15] and the psychopharmacological management of anxiety is complicated.[16] Adequate treatment trials for anxiety disorders in patients with bipolar disorder are uncommon, and the impact of mood-stabilizing treatments on anxiety is also unclear. It has been shown that patients with comorbid anxiety experience higher rates of mood instability than healthy controls[17] and that patients with comorbid anxiety and rapid mood switching might represent a genetically distinct subtype of bipolar disorder.[18] Our studies in bipolar disorder have found a negative cross-correlation between mood and anxiety;[7] thus, optimizing management of comorbid anxiety may be critical for strengthening mood regulation.

Another important variable closely linked to mood regulation is cognition. The costs of cognitive impairment in bipolar disorder have been described in all phases of the disorder,[19,20] including euthymia.[21] Patients in the depressive phase of the illness have reportedly experienced problems with both inhibiting the access of irrelevant negative material into working memory and disengaging from this material once it is no longer relevant.[22] In addition, rumination was reported to be an important predictor of depressive symptoms unique to bipolar disorder.[23] Inhibitory deficits may thus be a worthy target for cognitive remediation to improve mood regulatory capacities.

Rapid cycling and the pendulum

Can we better understand the dynamics of mood variability by assuming a priori the existence of an oscillator that might approximate the different polarities seen clinically? As hypomanic and depressive episodes occur periodically (unless effectively treated), we can model the mood variability of an untreated patient using a negatively damped harmonic oscillator.[13,14] An example of a simple harmonic oscillator would be a pendulum, as in a system that experiences a restoring force when displaced from its equilibrium position. If a frictional force (damping) proportional to velocity is also present, the harmonic oscillator is described as a damped oscillator. The model described by Daugherty and colleagues[13] conceptualizes treatment as a function forcing a stable limit cycle with smaller amplitude. Like any other model, it can help us picture some of the concepts related to illness and treatment. However, with some important elements not fully understood, it remains essentially a metaphor. Nevertheless, using these illustrations facilitates our understanding of complex processes and their application in clinical practice. In this case, for instance, it helps us conceptualize euthymic states in patients with bipolar disorder as mood fluctuations, but with a smaller amplitude (i.e., local fluctuations around a steady state).

Other authors modified the aforementioned model by inserting a time-dependent term, reflecting the interaction with the environment.[12] A good example for understanding this framework is antidepressant-induced rapid cycling: adding an antidepressant could be interpreted as an increase in oscillation frequency, facilitating the transition from local fluctuations around a steady state to the occurrence of episodes.

Modelling behavioural activation

Drawing on the theories of bipolar disorder that suggest the condition is underpinned by dysregulation of systems governing behavioural activation, some authors have proposed a mathematical model related to regulation of the behavioural activation system.[24] This is an interesting concept that describes the role of noise in bipolar disorder: increasing noise levels can lead to a transition from lower variability (local fluctuations in activation levels around a steady state) to higher variability (occurrence of episodes with lower local fluctuations). In contrast to other models,[25] this model proposes that illness progression does not inevitably lead to rapid cycling and chaotic behaviour. Rather, the increase of noise in the system could either lead to unstable behaviour with rapid fluctuations of behavioural activation levels (mirroring rapid cycling) or to a temporal fixation of activation levels in any of the states (mirroring depressive episodes; e.g., hypomanic or manic episodes), with a remaining susceptibility to slower variation among the three states. A clear example would be the effects of alcohol on mood. If we conceptualize alcohol as "noise," adding it to an already poorly calibrated system can lead to the occurrence of episodes with lower local fluctuations. In other words, the system will not be able to fluctuate around a steady state (i.e., an overall stable mood), but will keep itself at one of the three states (depression, mania or hypomania).

Clinical and research implications

The clinical course and longitudinal mood changes are an important dimension of psychopathology. Yet, they are largely absent both in the current DSM-5 criteria of mood disorders and in the Research Domain Criteria. Careful longitudinal observations in different diagnostic conditions and different mood states, as well as in healthy people, will be essential for better understanding the mechanisms involved and their clinical relevance. The paucity of healthy, normative data is a major gap that may challenge some of the preconceived ideas. For instance, in an earlier study we found that people with bipolar disorder who were in remission did not show more mood variability than healthy controls.[7] The main difference between the groups was in the nature of mood regulation: there was lower entropy of mood and energy series in

patients than in healthy controls. In keeping with this hypothesis of mood regulation being "less flexible" or more "rigid" in patients with bipolar disorder, our study of unaffected first-degree relatives showed a similar mood regulatory structure (lower entropy of mood and energy series) in both euthymic patients with bipolar disorder and in their unaffected relatives compared with healthy controls.[26] However, much larger samples and longer observations will be necessary to confirm these findings.

An in-depth study of mood (dys)regulation may also help answer the question of the association between different conditions with seemingly similar labile moods. One such matter is the issue of heterogeneity of bipolar disorder. Clinically, some patients experience severe and refractory abnormal mood states while others are characterized by labile "hyper-reactive" moods. Are these two extremes on a single continuum of mood dysregulation types, or do they represent distinct pathophysiologies responsive to different types of therapeutic interventions? Also clinically relevant will be our ability to modify the factors, such as anxiety or cognitive processes, that influence the sensitivity of mood regulatory systems.

Conclusion

Conceptualizing mood and mood disorders as regulated by complex, nonlinear systems can add new, relevant data to our daily clinical practice and may provide the clinician with better tools to treat and possibly anticipate major episodes. Complexity and related concepts should not be too distant from our clinical practice; they should be properly studied and understood for the benefit of our patients.

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