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Towards a complex system understanding of bipolar disorder: A map based model of a complex winnerless competition

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HIGHLIGHTS

- We proposed a novel discrete model of bipolar disorder based on notion of winnerless competition.
- Competitive maps represent the dynamics of activation in excitatory and inhibitory pathways.
- The model provides a theoretical framework addressing transition between two poles of the disease.
- The model represents the occurrence of rhythmic changes, rapid and ultra-rapid cycling of episodes.
- The model could also represent the manicogenic effects of antidepressants.

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ABSTRACT

Bipolar disorder is characterized by repeated erratic episodes of mania and depression, which can be understood as pathological complex system behavior involving cognitive, affective and psychomotor disturbance. In order to illuminate dynamical aspects of the longitudinal course of the illness, we propose here a novel complex model based on the notion of competition between recurrent maps, which mathematically represent the dynamics of activation in excitatory (Glutamatergic) and inhibitory (GABAergic) pathways. We assume that manic and depressive states can be considered stable sub attractors of a dynamical system through which the mood trajectory moves. The model provides a theoretical framework which can account for a number of complex phenomena of bipolar disorder, including intermittent transition between the two poles of the disorder, rapid and ultra-rapid cycling of episodes and manicogenic effects of antidepressants.

1. Introduction

Bipolar disorder is a lifelong, recurrent psychiatric condition associated with significant morbidity and mortality (López-Muñoz et al., 2006). The neurobiology of bipolar disorder is complex and poorly understood, with evidence supporting abnormalities of structure and/or function at many levels of the nervous system (Davidson et al., 2002; Goldbeter, 2011; Huber et al., 2000; Sanacora et al., 2012). One of the strongest domains of evidence relates to neurotransmitter function, with abnormalities in γ-aminobutyric acid (GABA) and glutamatergic pathways strongly implicated. A range of research also points to pathogenesis in the circadian system and abnormal patterns of corticocortical and subcortical connectivity (Berns and Nemeroff, 2003; Davidson et al., 2002; Goldbeter, 2011; Murray and Harvey, 2010; Pavuluri et al., 2005; Sanacora et al., 2012; Schloesser et al., 2012).

The time course of bipolar disorder is highly variable across patients, and highly variable within patients across the life span (Hadaeghi et al., 2013a; Huber et al., 2000). We sought to develop a mathematical model to shed some light on these apparently erratic variations. Such a model can be designed in a field of real or complex-valued properties extended over time, ruled by a set of coupled recurrent maps. Recurrent maps are receiving growing attention in the physics of complex systems (Courbage and Nekorkin, 2010; Girardi-Schappo et al., 2013; Ibarz et al., 2011; Rulkov et al., 2004). In discrete dynamical systems, or maps, each state is determined according to the states in previous finite time intervals (Hilborn, 2000), and the map based modeling approach seems to have potential for illuminating the inherently recursive pathological mood fluctuations in bipolar disorder.

From the perspective of nonlinear dynamics, manic and depressive phases of bipolar disorder can be considered two “strange sub-attractors” of a nonlinear dynamical system through which the mood

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trajectory moves (Hadaeghi et al., 2013a). Apparently erratic and abrupt changes of the mood state in bipolar disorder may be understood in terms of "chaotic intermittency" between these two sub-attractors (Hilborn, 2000; Tanaka et al., 2005). Within this framework, a simple model of a recurrent nonlinear system exhibiting various complex behaviors could provide a conceptual framework to examine the bistable intermittent states seen in bipolar disorder (Goldbeter, 2011; Huber et al., 2000).

We, therefore, developed a novel map based model of a chaotic system which accounts for the fundamental erratic time series of bipolar disorder through changes in the model's parameters. The model proposes that the highly complex and multi-dimensional states of mania and depression can be denoted through variables, which depend on the previous state and discrete exogenous and endogenous factors. Furthermore, in contrast to previous mathematical models of bipolar disorder (Daugherty et al., 2009; Goldbeter, 2011; Huber et al., 2000), we chose to define the emotional state as a complex number in which the real part represents the fluctuations around a depressive background, and the imaginary part symbolizes variations around a manic substrate. The vector quantity of emotional state in the complex manic-depressive plane is shown in Fig. 1A. By working from this assumption, the model can account for the mixed episodes which are prevalent in Bipolar I disorder, and for the combination of hypomania and depressive episodes seen in Bipolar II. Applying such a paradigm, the magnitude of the complex variable stands for severity of the state, and its angle quantitatively shows the mixture of manic and depressive symptoms. Importantly, it would be difficult to mathematically represent the mixed state if it were described by a real number only.

As discussed below, the model provides a theoretical framework addressing intermittent transition between two poles of the disease. The model also accounts for the occurrence of rhythmic mood state changes in the absence of external variation (i.e., endogenous rhythmicity) (Huber et al., 2000). Moreover, the model successfully represents rapid and ultra-rapid cycling of episodes, as well as the manicogenic effects of antidepressants (Damluji and Ferguson, 1988; Goldbeter, 2011; Papolos et al., 1998; Perlis et al., 2010; Tillman and Geller, 2003).

2. Model

In its general form, our phenomenological model is a simple linear recurrent map (Eq. (1)) in which the slope and the intercept change dynamically over time. Given that the system is thermodynamically open to external stimuli, the dynamic pattern of the variation in slope of the map is determined by external forces and environmental influences (Bauer et al., 2009). Meanwhile, the system internally reacts to external events by adjusting the dynamics of the intercept (see Fig. 2 for more details).

The key idea in designing the map is considering two poles of the disease as stable states (stable fixed points or sub-attractors) which are in a form of intermittent 'winnerless competition'. In ecological studies, the sequential unpredictable transitions of dominance between interacting species have been called a winnerless competition (Afraimovich et al., 2008; Rabinovich and Varona, 2011; Rabinovich et al., 2008, 2010, 2012). From the perspective of nonlinear dynamics, a mathematical image of these temporary 'victors' are saddle points, which attract the near trajectories along one direction and repel them along another direction in phase space (Hilborn et al., 1994). It has been suggested that this paradigm can explain dynamical phenomena in neuroscience, which have their roots in interactions between excitatory and inhibitory synaptic connections (Afraimovich et al., 2008; Rabinovich and Varona, 2011; Rabinovich et al., 2008, 2010, 2012).

$$z_{k+1} = a_k z_k + b_k \tag{1}$$

Fixed points of the map in each iteration, z_k^*, are related to the variable slope and intercept through the following rule:

$$z_{k+1} = z_k = z_k^* \to z_k^* = a_k z_k^* + b_k \to (1-a_k) z_k^* = b_k \to z_k^* = \frac{b_k}{(1-a_k)} \tag{2}$$

Therefore, have restricted a_k less than one, stability of the states over time will be ensured (Hilborn et al., 1994):

$$f'(z_k^*) = a_k \to \begin{cases} |a_k| < 1 & \text{Stable} \\ |a_k| > 1 & \text{Unstable} \end{cases}$$

In order to represent mutually inhibitory interactions among the poles of the disorder, we chose to relate the slope and the intercept of the map so that the fixed points of the system are arranged on the unit circle in the complex manic-depressive plane with some radians difference in their phase (Fig. 1B). Multistability is therefore, one of the characteristic features of the model, with winnerless competition explaining transitions between these stable states.

2.1. Multistability

A characterizing feature of some complex systems is "multistability", the coexistence of multiple interacting attractors (Chian et al., 2006). Various complex behaviors can emerge in the system's long term dynamics as a result of interactions among these attractors. The existence of multistability in nonlinear natural systems has previously been investigated in neuroscience, genetic networks, biological chemistry and population dynamics (Angeli et al., 2004; Attneave, 1971; Foss and Milton, 2000; Rabinovich et al., 2012). We propose that manic and depressive episodes in bipolar disorder can also be viewed as two stable state or sub-attractors of the recurrent map through which the mood trajectory moves (Hadaeghi et al., 2013a).

In the proposed system, multistability is achieved by arranging the fixed points of the map on the unit circle in the complex manic-depressive plane with a non-uniform distancing. Therefore, the stable fixed points would be mathematically described by the term $z_k^* = e^{i(k\pi(m/n)+\theta)}$ where m and n are integer numbers, the m/n ratio determines the number of stable states, and θ regulates the phase of

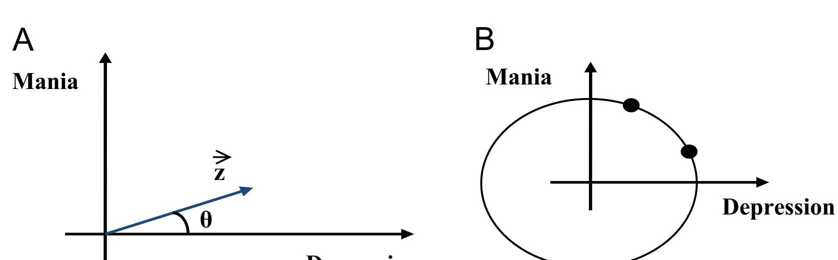

Fig. 1. (A) The vector quantity of the emotional state ($\vec{z}$) in the complex manic- depressive plane. (B) Schematic illustration of the way in which the stable fixed points (bold circles) of the map are arranged on the unit circle in the manic- depressive plane.