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A model for the dynamics of bipolar disorders

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ABSTRACT

Bipolar disorders are characterized by recurrent, alternating episodes of mania and depression. To examine the dynamical bases of this cyclical illness we consider a minimal model for bipolar disorders based on the observation that the two poles of the disease are mutually exclusive. We assume that the propensities to mania and depression, which are correlated with the activity of two putative neural circuits that promote, respectively, the manic or the depressive state, inhibit each other. When mutual inhibition is sufficiently strong, the model predicts bistability: the bipolar system is then either in a depressive or in a manic state and can display abrupt switches between these stable states. We consider two simple mechanisms which, when added to mutual inhibition, allow the model to pass from bistability to oscillations. Self-sustained oscillations provide a mechanism for the spontaneous, recurrent switching between mania and depression. The model can generate oscillations with a variety of waveforms, including simple periodic oscillations with comparable or unequal durations of the manic and depressive episodes, or small-amplitude oscillations around one of the two states preceding large-amplitude periodic changes in the propensities to mania or depression. The model provides a theoretical framework that covers the bipolar spectrum, i.e., cycling between the two poles of the disease, or evolution to either mania or depression or to an intermediate state without alternating between the two poles of the disease. The model accounts for the clinical observation that antidepressants can trigger the transition to mania or increase the frequency of bipolar cycling.

1. Introduction

Some mood disorders are conspicuous by their cyclical nature. The prototype of such cyclical illness is manic depression (Kraepelin, 1921), which is characterized by alternating episodes of mania and depression. This oscillatory mood disorder was initially described in the mid-XIXth century in France by Baillarger and Falret, who independently proposed that mania and depression were different expressions of the same disease, that they called « folie à double forme » (Baillarger, 1854) or « folie circulaire » (Falret, 1854). Because of the cycling between these two opposite states, the illness is referred to as "bipolar disorder" (Goodwin and Jamison, 2007; Soares and Young, 2007).

Although some progress has been made on the elucidation of the underlying mechanism and the development of treatments, the molecular and cellular bases of bipolar disorders remain largely unknown (Soares and Young, 2007; Barnett and Smoller, 2009). Advances based on the use of brain imaging techniques such as functional MRI nevertheless begin to shed light on the neuroanatomy of bipolar disorder (Blumberg et al., 2003; Cerullo et al., 2009; Soares, 2003; Strakowski et al., 2005; Townsend et al., 2010). Many of these studies point to the involvement of neural circuits located in the prefrontal cortex with connections in the amygdala, striatum and thalamus (Blumberg et al., 2004; Chepenik et al., 2010; Foland et al., 2008; Womer et al., 2009). Several lines of evidence establish a link between disruptions of the circadian clock and mood disorders (Healy and Waterhouse, 1995; McClung, 2007) including manic (Roybal et al., 2007) or depressive behavior (Wehr et al., 1979). A key feature is the tight link between mania and depression, which appear to form the two extreme conditions of a common disease spectrum (Katzow et al., 2003). That the two poles are linked is further suggested by the observation that antidepressants can trigger the transition to mania or increase the frequency of bipolar cycling (Altshuler et al., 1995; Goldberg and Truman, 2003; Goodwin and Jamison, 2007; Truman et al., 2007).

The purpose of this paper is to examine the types of mechanism that are capable of accounting for the cyclic alternation between mania and depression. To this end a minimal, qualitative model is proposed for the dynamics of bipolar disorders. The model allows us to determine the conditions in which cyclical transitions between mania and depression may occur. It provides a framework

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that covers the whole bipolar spectrum: in some conditions the bipolar system may cycle between the two poles of the disease, while in other conditions it is locked in either the manic or depressive states, without alternating between them. We will use the model to probe the effect of antidepressants, which can induce the transition to mania or accelerate bipolar cycling.

2. A model for bipolar disorders

To build the model for bipolar disorders we first focus on the observation that, at least in their extreme manifestations, the two poles of the disease are mutually exclusive: the patient is either depressive or in a manic state. Such a situation is reminiscent of bistability. In a second stage we investigate how repetitive transitions may occur between the two extreme poles of the disease. Self-sustained oscillations provide a mechanism for the spontaneous switching between mania and depression. We determine the ingredients needed to extend the model so that it may pass from bistability to oscillations. Finally we use the model to investigate the paradoxical effect of antidepressants, which can trigger the transition to mania or induce rapid bipolar cycling.

2.1. From monostability to bistability in bipolar disorders

Our goal is to propose a phenomenological model, as simple as possible, that can account for the dynamics of bipolar disorders. The observation that mania and depression exclude each other suggests that such mutual inhibition can lead to *bistability* in which two stable steady states, separated by an unstable steady state, coexist in a given set of conditions. Bistability is a well-known property of nonlinear systems in chemistry and physics. The phenomenon has also been observed at different levels in biological systems where it often originates from mutual inhibition (see section 3). In developing the model for bipolar disorders, we first address the conditions in which it displays bistability, before investigating its capability to produce a cyclical alternation between mania and depression.

Related to the two poles of the disease, the variables of the core model for bistability are the propensities to mania (M) and depression (D). Mania and depression are highly complex traits that have multiple dimensions. We nevertheless make the assumption that they can be represented by continuous variables, even if there is no straightforward manner to measure them clinically in such a way at this stage. This simplifying assumption is retained because we wish to explore the dynamical bases of the disorder in a qualitative model, as simple as possible, based on ordinary differential equations. Key to the model is the coupling between the variables M and D. A variety of direct or indirect interactions between M and D could lead to bistability. Here we focus on the case of mutual inhibition and assume that the rise in M prevents the rise in D, and vice versa. This hypothetical mechanism is supported by the observation that antidepressants, which decrease D, can induce the transition to mania, as if the latter were held in check by the depressive state. Such mutual inhibition can be implemented in many ways. The particular choice of mathematical formalism is less important here than the type of regulation, as attested by a variety of examples of bistability arising from mutual inhibition, in fields ranging from neurobiology and genetic networks to population biology (see section 3). We adopt a biochemical formalism, which resembles that used in population biology and was previously shown to provide useful insights in a neurobiological context for analyzing the qualitative dynamics of thalamic neurons (Goldbeter and Moran, 1988; Llinas, 1988). This approach is further justified by the fact that the molecular and cellular mechanisms underlying the onset of mania and depression remain largely unknown. The propensities to mania and depression are likely correlated with the levels of particular neurotransmitters or electrical activities generated by two neural circuits, the functioning of which promotes either the manic or the depressive state.

The model for bistability in bipolar disorders is schematized in Fig. 1. The propensities M and D, defined as positive quantities, both have a source and a sink, and inhibit the build up of the other variable. Their time evolution is governed by the ordinary differential equations (1a) and (1b). Parameters V_M and V_D are the maximum rates at which mania and depression build up, while k_M and k_D measure the maximum rates at which M and D disappear. The sink for M and D is described by a function of the Michaelis–Menten type where K_1 and K_2 denote, respectively, the values of M and D corresponding to the half-maximum rate of their disappearance. The two equations are coupled through the terms describing mutual inhibition, which is expressed by means of Hill functions. Thus, in eqs. (1a) and (1b), K_{i1} denotes the value of D yielding 50% inhibition of M, while K_{i2} represents the value of M yielding 50% inhibition of D. To reflect the nonlinearity of the feedback, we take a value of 2 for the Hill coefficients that characterize the cooperative nature of the inhibitory processes. Similar results are obtained for larger values of the Hill coefficient.

$$\frac{dM}{dt} = V_M\left(\frac{K_{i1}^2}{K_{i1}^2 + D^2}\right) - k_M\left(\frac{M}{K_1 + M}\right) \tag{1a}$$

$$\frac{dD}{dt} = V_D\left(\frac{K_{i2}^2}{K_{i2}^2 + M^2}\right) - k_D\left(\frac{D}{K_2 + D}\right) \tag{1b}$$

2.1.1. Monostability

When the inhibition constants K_{i1} and K_{i2} are sufficiently large, i.e., when mutual inhibition is weak, numerical simulations indicate that the system of equations (1a) and (1b) admits a single steady-state solution, which is stable. Then, upon increasing the value of parameter $\theta = V_D/V_M$, D progressively increases while M diminishes. Starting from a low value of θ, the steady state continuously changes from a situation where M predominates over D to the reverse situation (Fig. 2).

The curves showing the steady-state levels of M and D in Fig. 2 are not drawn at the same scale and are not symmetric, since θ varies by increasing V_D while holding V_M at a fixed value. In the case considered, because all other parameters have similar values in the kinetic equations for M and D, identical steady-state values are obtained for the two variables when $V_D = V_M$, i.e., when $\theta = 1$.

2.1.2. Bistability

In contrast to this situation where a single steady state exists, bistability can be observed when the values of K_{i1} and K_{i2} are sufficiently low, i.e., when the strength of mutual inhibition is sufficiently large (Fig. 3). In a range bounded by two critical values of the parameter $\theta = V_D/V_M$, two stable steady states then coexist. In one stable state (lower branch of D in Fig. 3A and upper branch of M

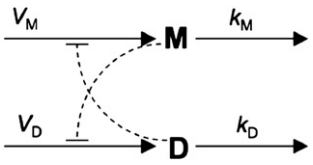

Fig. 1. Scheme of the model for bistability in bipolar disorders. M and D represent the propensity toward mania and depression. Parameters V_M, k_M and V_D, k_D measure the rates of build up and disappearance of M and D, respectively. The key assumption is that M and D inhibit each other (dashed lines). Such mutual inhibition results either in monostability (Fig. 2) or bistability (Fig. 3).