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On the impact of episode sensitization on the course of recurrent affective disorders

Martin Tobias Huber [a,*], Hans Albert Braun [b], Jürgen-Christian Krieg [a]

[a] *Department of Psychiatry and Psychotherapy, University of Marburg, Rudolf-Bultmannstr. 8, D-35033 Marburg, Germany*
[b] *Institute of Physiology, University of Marburg, Rudolf-Bultmannstr. 8, D-35033 Marburg, Germany*

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Abstract

Sensitization of an organism by recurrent disease episodes is postulated as a key mechanism governing the progressive long-term course of affective disorders. The particular significance is that episode sensitization could underly the transition from externally triggered disease episodes to autonomous episode generation. Functionally, this transition might be explained by positive feedback between a disease episode and the activity state of an organism which includes the introduction of a memory trace for generated disease episodes. Here we consider the functional consequences of episode sensitization for the course of recurrent affective disorders. We use a computational approach and extend our previously introduced model for the course of affective disorders by a feedback mechanism for episode sensitization. Depending on sensitization timescale and amount, triggered episodes leave the model in a sustained sensitized state or induce autonomous disease progression. Runaway activation can end in saturation. Remarkably, however, over a broad parametric range the progression ends in intermediate states with fluctuating disease patterns. This behavior results from the model's nonlinear dynamics and represents a situation where the feedback intermittently changes between positive and negative directions. Our simulations strongly support episode sensitization as an important disease mechanism for affective disorders. From a nonlinear standpoint, this mechanism offers an explanation not only for autonomous disease progression but also for occurence and stability of irregular rapid-cycling disease states.

Keywords: Affective disorders; Episode sensitisation; Kindling; Dynamic disease; Nonlinear dynamics; Computational model

1. Introduction

Recurrence and progression characterize the long-term course of uni- and bipolar affective disorders. Almost all bipolar disorders are recurrent and most patients with unipolar disorders will have recurrences. The disorders tend to take a progressive course reaching from isolated episodes at the beginning to rhythmic episode occurences and finally rapidly changing irregular mood states (Kraepelin, 1921; Post, 1992; Post and Weiss, 1995; Kramlinger and Post, 1996; Keller and Boland, 1998; Kessing et al., 1998, a–d).

Kindling and Sensitization are related paradigms that have been used to explain the recurrent and progressive course of affective disorders (Post, 1992). In kindling, epileptic seizures are initially elicited by electrical or chemical stimuli, but, after a sufficient number of seizures, a progression to spontaneity occurs. In a similar way, affective disease episodes could sensitize an organism with the result of autonomous illness progression (Post and Weiss, 1995, 1998; Ghaemi et al., 1999).

This mechanism is referred to as episode sensitization (Fig. 1a). It is based on the clinical observations that initial episodes can be related to psychosocial stressors but that this influence decreases on subsequent episodes (Post, 1992; Post and Weiss, 1995, 1998; Keller and Boland, 1998). In addition, the duration of time until recurrence decreases as a function of the number of prior episodes suggesting that disease episodes themselves have an impact on the course of the disease. So far, the majority of clinical studies investigating recurrence in affective disorders observed a deteriorating course in both unipolar and bipolar disorders (a summary of studies is given by Table 1 in Kessing et al., 1998c). The best evidence for episode sensitization thereby is probably provided by the recent Danish case register study, where the

* Corresponding author. Tel.: +49-6421-285221; fax: +49-6421-288939.
E-mail address: huberm@mailer.uni-marburg.de (M.T. Huber).

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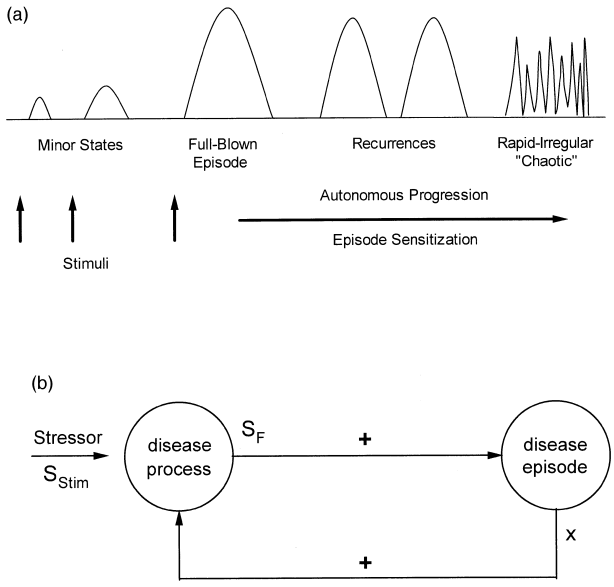

Fig. 1. (a) Episode sensitization might cause a transition from triggered episodes to autonomous disease progression (modified after Post et al., 1986; Post and Weiss, 1995). (b) Episode sensitization represents positive feedback between disease process and disease episode.

rate of recurrence after successive episodes was calculated in a sample of 20 350 patients (Kessing et al., 1998c,d). The study clearly demonstrates an increasing risk for recurrence with every new episode in both unipolar and bipolar disorder and indicates the deteriorating effect of the illness process itself. Notably, the same deteriorating course was observed as in the pre-drug era (Kraepelin, 1921). Thus, understanding the mechanisms and effects of episode sensitization seems to be a necessary step towards understanding the pathophysiology of affective disorders.

The neurobiological correlates of episode sensitization can reasonably be assumed to be complex. Similar as observed in kindling experiments (see Fig. 1 in Post, 1992), a variety of neuroplastic changes reaching from acute events to immediate early gene expression to anatomic changes has to be expected. In this way each disease episode can implement a long-lasting memory trace into the neurobiology of a respective organism (Post, 1992; Post and Weiss, 1995). From a functional standpoint two issues are relevant. First, episode sensitization represents *positive feedback* between a disease system and its respective disease episode. Second, the implementation of a longlasting memory trace requires the introduction of a new additional *slower timescale* when compared to the timescale of disease episodes. It is the subject of this paper, to investigate the consequences for the course of affective disorders that arise out of these, at first glance, rather simple functional properties of episode sensitization.

Our starting point is to consider a disease system and its output, the disease episode, as the two parts of a positive feedback loop. Appropriate activation of the disease system will result in initiation of disease episodes and the disease episodes in turn will stimulate or *sensitize* the disease system. The positive direction of the feedback together with the slow timescale ultimately leads to autonomous disease progression which will continue until some sort of saturation is approached.

However, a problem arises. Cycle acceleration often ends in apparently irregular, rapidly changing mood patterns which obviously cannot be considered as a saturated state. Further, this prototypical timecourse rather naturally prompts consideration of nonlinear dynamics as a way to analyze and conceptualize affective disorders (Ehlers, 1995; Gottschalk et al., 1995; Post and Weiss, 1995; Kramlinger and Post, 1996; Woysville et al., 1999). The reason is that oscillatory nonlinear systems with three or more variables (dimensions) are well-known to respond to stimulation with frequency increase but, after a critical level of stimulation, bifurcations (abrupt shifts in behaviour on small parameter changes) to chaotic behaviour can occur (Baker and Gollub, 1990; Strogatz, 1994). Hence, the observed clinical course as well as implications from dynamical systems theory pose a limit on the abovementioned simple scenario. Therefore, one is tempted to ask, if and how the dynamic principles underlying episode sensitization can indeed offer a template for understanding the origin of the clinically observed disease courses.

So far, despite the obvious clinical relevance, the dynamical aspects of episode sensitization have not been studied (for a cognitive science perspective on kindling and episode sensitization see Segal et al., 1996). In part, this might be due to the neurobiological complexity which prevents building a detailed quantitative model. However, we found it not to early to try to assess the possible impact of such a sensitization process on the progression of affective disorders. To do this, we use and extend a simple phenomenological model for timecourse and disease patterns of affective disorders recently introduced by us (for a detailed description of the model please see Huber et al., 1999; 2000a).

The model is based on a mathematical description of nonlinear oscillatory dynamics, as commonly used in neuronal modelling studies. In principle, the model generates transient activity events, the "disease episodes", in dependence on an activation parameter, the "ongoing disease process". Increasing the value of the activation parameter results in cycle acceleration until bifurcations to chaotic activity occur. In the present study we extend this model by a dynamic mechanism accounting for episode sensitization. Using computer simulations, we study the effect of episode sensitization on disease progression in the model. We demonstrate that episode sensitization, when implemented in a nonlinear disease model, leads to autonomous disease progression ending in irregularily fluctuating disease states. We determine the