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On Episode Sensitization in Recurrent Affective Disorders: The Role of Noise

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Episode sensitization is postulated as a key mechanism underlying the long-term course of recurrent affective disorders. Functionally, episode sensitization represents positive feedback between a disease process and its disease episodes resulting in a transition from externally triggered to autonomous episode generation. Recently, we introduced computational approaches to elucidate the functional properties of sensitization. Specifically, we considered the dynamics of episode sensitization with a simple computational model. The present study extends this work by investigating how naturally occurring, internal or external, random influences ('noise') affect episode sensitization. Our simulations demonstrate that actions of noise differ qualitatively in dependence on both the model's activity state as well as the noise intensity. Thereby induction as well as suppression of sensitization can be observed. Most interestingly, externally triggered sensitization development can be minimized by tuning the noise to intermediate intensities. Our findings contribute to the conceptual understanding of the clinical kindling model for affective disorders and also indicate interesting roles for random fluctuations in kindling and sensitization at the neuronal level.
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INTRODUCTION

Kindling and episode sensitization are two related phenomena that offer a framework to understand the longitudinal course of recurrent affective disorders. In kindling, epileptic seizures are initially related to stimuli but after a sufficient number of seizures, a progression to spontaneity occurs (see eg Kraus, 2000 and literature therein). Similarly, initial disease episodes of affective disorders can often be related to psychosocial stressors but this influence decreases on subsequent episodes resulting in apparently autonomous disease progression. In spite of a large variability in individual time courses, the abstracted general principle is that illness patterns thereby change from isolated episodes to more rapid, rhythmic patterns, and finally ultrafast 'chaotic' mood oscillations (also referred to as rapid and ultrarapid cycling disease states, see the discussion in Post and Weiss (1995)). This clinically derived phenomenon is referred to as episode sensitization (Post *et al*, 1986; Post, 1992; Post and Weiss, 1995; Kessing *et al*, 1998; Huber *et al*, 2001a, and literature therein). Various neuroplastic changes, such as expression of immediate-early genes or neuronal sprouting, are observed during kindling evolution and similar adaptive changes might also determine the neurobiogical changes underlying episode sensitization in affective disorders (Post and Weiss, 1995, 1998; Ghaemi *et al*, 1999; Kraus, 2000).

We recently considered episode sensitization with a computational model (Huber *et al*, 2001a, b) which, similar to the kindling approach to affective disorders (Post, 1992), is based on a nonhomologous neuronal analogy (see also Methods). In this model, external stimulation generates transient events (the 'disease episodes') and each of the events feeds back positively thereby exerting a sensitizing influence that can lead to autonomous disease progression. Interestingly, these nonlinear feedback interactions also offer an explanation for the occurrence as well as the stability of rapidly changing 'chaotic' disease states (Huber *et al*, 2001a). In earlier modelling studies, we have also examined the effects of naturally occurring random influences, that is, noise, for the time course of affective disorders (Huber *et al*, 1999, 2000). However, the impact of noise has not been considered so far with regard to episode sensitization and kindling although it can be expected that slight random fluctuations might also become important with respect to a sensitization process. The reason is that the positive feedback associated with sensitization might significantly amplify such random fluctuations and vice versa.

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A huge amount of literature exists on stochastic effects in various natural systems (eg see Wiesenfeld and Moss, 1995; Bulsara and Gammaitoni, 1996; Tuckwell, 1988) and there are many reports from very different levels of biological systems demonstrating their physiological relevance. The most famous example is *stochastic resonance* (SR) where noise does not simply represent a nuisance but can optimize the detection of weak stimuli. SR is qualitatively good to understand when one considers a weak, subthreshold stimulus delivered to a threshold element such as a neuron. Without noise, the signal is not detectable. In this case, the addition of an appropriate amount of noise is helpful. It is easy to understand that an optimal noise level exists because too little noise leaves the signal undetected whereas too much noise smears the signal.

SR and other cooperative noise effects so far have been extensively studied in very different fields reaching from protein switches and ion channels dynamics (Gardner *et al*, 2000; Hasty *et al*, 2000; Bezrukov and Vodyanoy, 1995; Astumian *et al*, 1997; Petracchi *et al*, 1994), to membrane currents and action potential generation (Douglass *et al*, 1993; Braun *et al*, 1980, 1994; Huber *et al*, 1998; White *et al*, 1998; Longtin *et al*, 1991; Levin and Miller, 1996; Gluckman *et al*, 1996; Stacey and Durand, 2000; Rudolph and Destexhe, 2001), to cognitive functions and behavioral responses (Stemmler *et al*, 1995; Simonotto *et al*, 1997; Winterer *et al*, 1999; Russell *et al*, 1999; Freund *et al*, 2001, 2002), and also with regard to different aspects of psychiatric disorders (Huber *et al*, 1999, 2000; Winterer *et al*, 2000).

Accordingly, psychiatrically relevant noise sources also appear at various levels. For example, neuronal activity in the brain is inherently noisy because of random ion channel dynamics and stochastic synaptic input. For a detailed discussion of noise in neuronal systems, see for example, Longtin and Hinzer (1996) and Tuckwell (1988) as well as White *et al* (1998, 2000) and Huber *et al* (1998) with respect to oscillatory neurons. Moreover, random fluctuations of RNA concentration and protein expression might contribute to long-lasting neuroplastic sensitization effects. Similar effects might also occur at the systems level, especially in humoral control where, for example, disturbances in the hypothalamic–pituitary–adrenal (HPA) axis seem to be of particular significance for affective disorders (Holsboer, 1995; Holsboer *et al*, 1995). Finally, at the behavioral level, individuals face a variety of life stress, which differs in strength and impact and reaches from everyday hassles to social isolation up to the loss of significant others. In turn, such life stress might be viewed as a complex variable 'noisy environment' that individuals have to deal with and which will interact with any disease process (Glassner and Haldipur, 1983; Kennedy *et al*, 1983; Bidzinska, 1984; Ambelas, 1987; Swann *et al*, 1990; Charney *et al*, 1993; Castine *et al*, 1998).

The present paper aims to elucidate some principal noise effects on sensitization processes. Being aware of the complexity of the underlying biology, our model is extremely simplified not only with regard to the number of variables but also with regard to the many potential noise sources. The latter are represented in the first approximation by Gaussian white noise with a single parameter determining the noise intensity. In spite of these simplifications, we demonstrate that stochastic fluctuations can have significant effects on sensitization processes which, to a major part, are unexpected within a conventional perspective. Our simulations show that the effects of noise critically depend on the actual dynamical state of the system as well as on the noise intensity. We will demonstrate that increasing noise, as intuitively might be expected, can facilitate sensitization on subthreshold states of the model, which clinically would correspond to a situation before the manifestation of disease episodes. The study further demonstrates that noise can also suppress the development of sensitization in situations where, without random influences, an autonomous disease progression would be the ultimate result. In this case, tuning of the noise to intermediate intensities can minimize sensitization.

METHODS

We use the sensitization model as described in detail in our previous paper (Huber *et al*, 2001a; see also Huber *et al*, 1999, 2000 for the model without sensitization). However, a brief description of the model as well as the defining equations are provided here. For the purpose of our modeling studies, we adapted a generalized description for intrinsic biological rhythmicity and event generation as it is commonly used in neuronal modeling (Arbib, 1995). Importantly, such descriptions contain different nonlinear excitatory and inhibitory elements that operate at different time scales and activation levels. Interaction of these elements leads to a variety of dynamical behaviors, including stable states, periodic and quasiperiodic oscillations, and chaos (Chay *et al*, 1995). This modeling approach, similar to the kindling approach, represents a nonhomologous neuronal analogy to disease patterns and course of recurrent affective disorders, and the mathematical formalism used is based on that used for neuronal oscillators (Wang, 1993; Wang and Rinzel, 1995; Chay *et al*, 1995; Huber *et al*, 1998; a more detailed discusssion of our modeling approach to affective disorders is given in Huber *et al*, 1999, 2000).

The behavior of our specific model results from the interactions of two activity-dependent subsystems together with a sensitization loop. On activation by an external stimulus and/or noise, the first subsystem generates low-amplitude oscillations in the model activity whereas, on higher levels of activation, the second subsystem generates transient high-amplitude events ('disease episodes'). The sensitization loop represents *positive feedback* between the activity of the model and a sensitization variable and where the feedback loop is closed during the generation of transient events ('episode sensitization'). Importantly, the sensitization acts on an additional and much slower timescale when compared to the timescale of our model disease episodes. Therefore, once activated, the sensitization loop can lead to autonomous event generation, depending on the sensitization time scale and amount (Figure 1).

The overall behavior of the model is described by changes in the activity variable x given by the differential equation

$$\tau_x \, dx/dt = -x - \sum_i a_i^y w_i (x - x_i) + S_F + S_{\text{Stim}} + gw, \quad (1)$$

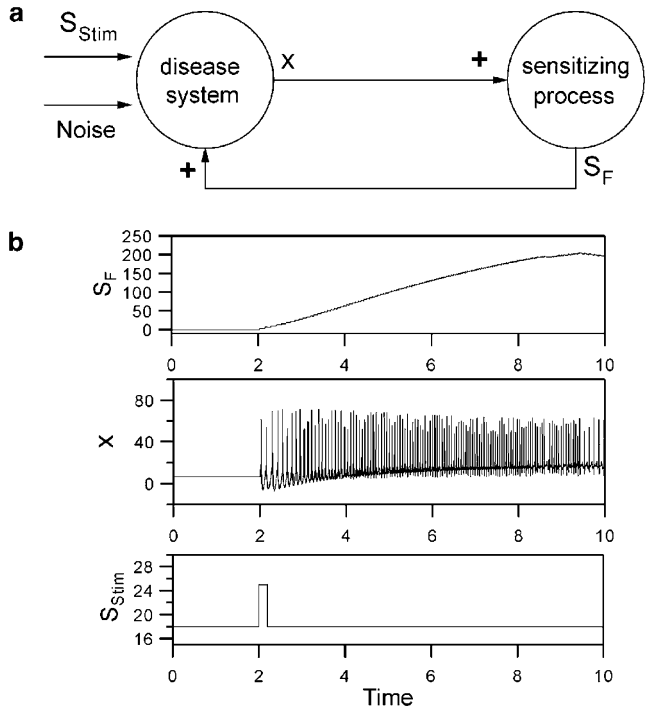

Figure 1 (a) Schematic representation of episode sensitization as implemented in the model. S_{Stim} is an external stimulus, x the activity of our model, and S_F the sensitization variable. (b) Time traces of a simulated sensitization run (activity x, sensitization variable S_F, and external stimulus S_{Stim}). The step stimulus generates transient events ('disease episodes'). The following event-dependent activation of the sensitization loop then results in autonomous event generation.

with τ_x being a time constant, a_i^ν the activation states of two excitatory and two inhibitory elements of the respective two oscillators ($\nu = 1$ except for a_{he}—see below—where $\nu = 2$) with a_{hi} and a_{he} the rapid high-threshold activating elements (transient events) and a_{li} and a_{le} the slow low-threshold activating elements (slow periodicities). The w_i are the coupling constants and the x_i are the activation levels. S_F is the sensitization variable, the parameter S_{Stim} represents an external activating stimulus (eg external stressors) and gw denotes Gaussian white noise with zero mean (see below). The changes in activation states are given by

$$\tau_i \, \mathrm{d}a_i/\mathrm{d}t = F_i(x) - a_i, \tag{2}$$

with τ_i being the time constants and with sigmoidal steady-state activation functions $F_i(x) = 1/\{1 + \exp(-\Delta_i(x - x_{i,0.5}))\}$ with Δ_i the steepness and $x_{i,0.5}$ the half-activation levels. The sensitization variable S_F is given by $S_F = S_{\max} a_S$ with $S_{\max}$ determining the maximum amount of sensitization and with a_S being an activation variable that can vary between zero and 1 depending on the activity x. The change in a_S is given by

$$\tau_S \, \mathrm{d}a_S/\mathrm{d}t = F_S(x) - a_S, \tag{3}$$

with τ_S being a relaxation time constant. $F_S(x) = 1/\{1 + \exp(-\Delta_S(x - x_{S,0.5}))\}$ again is a sigmoidal activation function with Δ_S the slope and $x_{S,0.5}$ the half-activation value.

Stochastic influences are accounted for by the term gw that represents Gaussian white noise with zero mean, and is calculated according to the Box–Mueller algorithm (Fox *et al*, 1988)

$$gw = (-4D \, \mathrm{d}t \, \ln(a))^{1/2} \cos(2\pi b), \tag{4}$$

where a and b are random numbers (0–1). The noise intensity is adjusted by the dimensionless parameter D (variance $\sigma^2 = 2D \, \mathrm{d}t$) and numerical implementation of gw is as described in Fox *et al* (1988):

$$x_{t+\mathrm{d}t} = x_t + g(x) \, \mathrm{d}t + gw, \tag{5}$$

where $g(x) = (-x - \sum a_i^\nu w_i \, (x - x_i) + S_F + S_{\text{Stim}})/\tau_x$.

The system of differential equations has been solved numerically with a forward Euler integration method with step size adjusted to 0.1 time units (Mascagni, 1989). Accuracy and stability was tested by adjusting the step size to smaller values. Additional testing of numerical results was performed by comparison with integration using the standard Runge–Kutta fourth-order numerical integration method. The parameters of interest here are the noise intensity D and the external stimulus S_{Stim}. Additional exploratory simulations were performed at different parameter constellations for the sensitization mechanism ($S_{\max}$, τ_S, and Δ_S). Similar behaviors were obtained as the ones shown in the results section, indicating the generality of the observed findings. For consistency and comparison, similar numerical values were chosen here as in our previous sensitization studies (Huber *et al*, 1999, 2000, 2001a, b). A dimensionless set of units is used and numerical values for the simulations are: $\tau_x = 10$, $w_{\text{hi}} = 20$, $w_{\text{he}} = 15$, $w_{\text{li}} = 18$, $w_{\text{le}} = 3$, $x_{\text{hi}} = x_{\text{li}} = -30$, $x_{\text{he}} = x_{\text{le}} = 110$, $\tau_{\text{hi}} = 2$, $\tau_{\text{he}} = 0 (\mathrm{d}a_{\text{he}}/\mathrm{d}t = 0$ thus $a_{\text{he}} = F_{\text{he}}(x))$, $\tau_{\text{li}} = 50$, $\tau_{\text{le}} = 10$, $\Delta_{\text{he}} = \Delta_{\text{hi}} = \Delta_{\text{li}} = \Delta_{\text{le}} = 0.25$, $x_{\text{hi},0.5} = x_{\text{he},0.5} = 35$, $x_{\text{li},0.5} = x_{\text{le},0.5} = 20$, $\Delta_s = 10$, $x_{s,0.5} = 35$, $\tau_s = 5000$, $S_{\max} = 5000$.

RESULTS

Our starting point is the sensitization model as described for fully deterministic conditions in Huber *et al* (2001a) and with the relevant sensitization parameters set to $S_{\max} = 5000$ and $\tau_S = 5000$. Without stimulation ($S_{\text{Stim}} = 0$ and $D = 0$), the model remains at its resting state. Application of a single external suprathreshold stimulus ($S_{\text{Stim}} = 25$, with duration $T_P = 200$ time units) triggers a single pair of transient events, which in turn are sufficient to turn on the sensitization loop. The result is an ongoing generation of events or, in other words, an 'autonomous progression' (Figure 1b).

To illustrate the effects of noise on such a sensitization process we first consider the behavior of the model without stimulus-induced event generation and compare how noise modifies the system's behavior in a stable and in an already vulnerable state (not activated *vs* slightly activated). Then we investigate the system's behavior when subjected to an external step stimulus, that is, mimicking a stressor, and consider the noise effects at different amplitudes of the stimulus. Finally, we consider in more detail the situation where an external stimulus results in sensitization and demonstrate that in this situation tuning of the noise to intermediate intensities can minimize sensitization.

Noise-Mediated Sensitization

We consider the sensitization model *without* stimulus-induced event generation but with two different levels of continuous subthreshold activation ($S_{Stim} = 0$ and 18). When the model is at rest ($S_{Stim} = 0$), addition of noise ($D = 0.12$) only causes some random fluctuations around the resting state (Figure 2a, upper two traces). The situation much changes when the model is slightly activated ($S_{Stim} = 18$, Figure 2a, lower two traces). Although, the model, under deterministic conditions, is still at rest, addition of a moderate amount of noise has a profound effect as it mediates oscillatory activity. The reason is that the model now is close to a transition to subthreshold oscillations where noise can induce transitions to this oscillatory state (see also Huber *et al*, 1999, 2000 for noise-induced state transitions in the model without sensitization, for noise-mediated *coherence resonance* effects, ie SR without a periodic stimulus, see eg Gang *et al*, 1993; Lee *et al*, 1998; Neiman *et al*, 1997).

Such noise effects can become of particular relevance for sensitization and disease progression. This is the case when the subthreshold oscillations, just by chance, reach the threshold of event generation (Figure 2b, left trace). Once event generation takes place, the sensitization mechanism becomes activated. The positive feedback between activity x and sensitization variable S_F can result in an autonomous progression of event generation or 'autonomous episode recurrence' within a disease context. However, in the presence of noise, sensitization is not fully deterministic but occurs with a certain probability that depends on the noise intensity. This is shown in Figure 2b, right trace. In this figure, the results are shown from simulation runs where for each value of the noise intensity D, a total of 1000 simulation runs were performed and the number of successful sensitizations (Counts) was determined. As shown in Figure 2b, the relation between noise intensity D and the probability of 'autonomous progressions' exhibits the typical probabilistic sigmoidal function (Figure 2b, right trace).

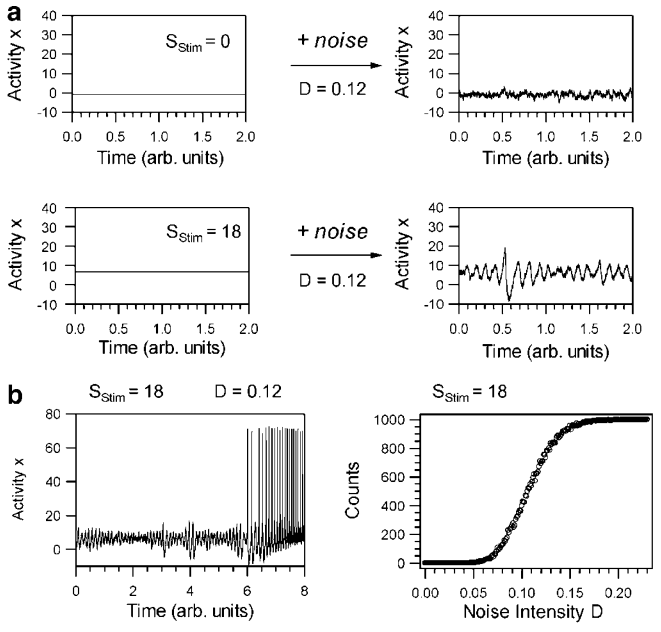

Figure 2 Noise-mediated sensitization without a stimulus. (a) When the model is fully at rest, added noise only leads to minor fluctuations of the activity (upper traces). In contrast, when the model is slightly activated, added noise induces pronounced oscillatory responses (lower traces). (b) The noise-induced oscillatory activity can reach the threshold for event generation, in this way starting the sensitization evolution. The relation between the number of successful sensitization runs (counts) *vs* the intensity D of the noise is sigmoidal (right trace). For each value of the noise intensity D (increment $\Delta D = 0.001$), a total of 1000 simulation runs was performed (duration $T = 20\,000$ time units for each run), and the number of successful sensitization progressions, denoted as counts, was determined.

Noise Effects on Stimulus-Triggered Sensitization

We now consider the clinically important situation where first disease episodes are triggered by external stressors. For that we apply S_{Stim} as an activating step stimulus to our model as shown in the examples of Figure 3. In all cases, $S_{Stim} = \max S_{Stim}$ for a stimulation period of $T = 200$ time units, otherwise $S_{Stim} = 18$ (stimulus baseline). Only the amplitude of the step stimulus was varied (different levels of $\max S_{Stim}$) and the effects under deterministic and noisy conditions are compared ($D = 0$ *vs* 0.05).

Under deterministic conditions, we observe two principal behaviors: (i) relaxation back to the resting state, when stimulation is too weak (Figure 3a, $\max S_{Stim} = 23$, upper

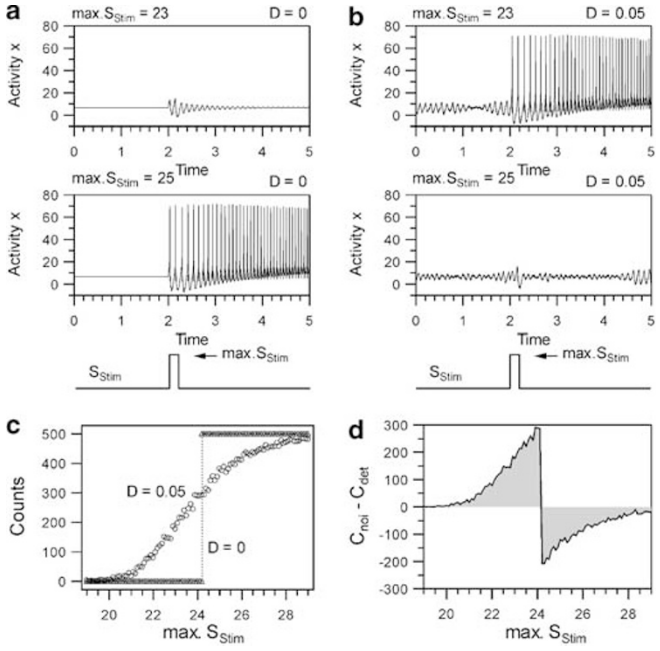

Figure 3 Noise effects on stimulus-triggered sensitization. A step stimulus S_{Stim} of duration $T_S = 200$ time units was applied to the model system. The baseline value of step stimulus is $S_{Stim} = 18$ in all simulations. The maximum value of the step stimulus, $\max S_{Stim}$, was varied systematically as indicated in the figure. The simulations were performed under fully deterministic conditions ($D = 0$) and with the addition of noise ($D = 0.05$). (a) Activity traces under deterministic conditions for two different values of $\max S_{Stim}$. (b) Activity traces from noisy simulations. (c) Counts of successful sensitization runs *vs* the maximum value of the step stimulus $\max S_{Stim}$ (per 500 runs, each run with duration $t = 20\,000$ time units and with increment for $\Delta \max S_{Stim} = 0.1$). Deterministic case: triangles and dashed line; noisy case: circles. (d) Plot of the difference between deterministic and noisy response functions, $\Delta\text{Counts} = C_{noi} - C_{det}$.

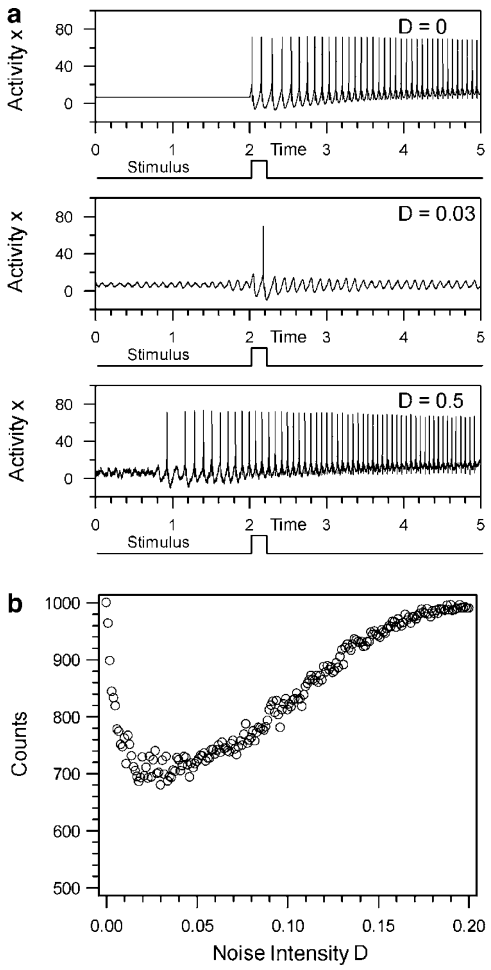

Figure 4 Tuning of the noise intensity minimizes sensitization development. (a) Sensitization experiments under deterministic conditions ($D = 0$) and for two different levels of the noise intensity ($D = 0.03$, $D = 0.5$). Baseline stimulus $S_{Stim} = 18$ and $\max S_{Stim} = 25$ in all cases. (b) Counts of successful runs plotted *vs* noise intensity D. The curve passes through a minimum on subsequent increases of the noise intensity.

trace) and (ii) autonomous progression of event generation because of sustained activation of the sensitization mechanism (Figure 3a, $\max S_{Stim} = 25$, lower trace). The transitions between the two behaviors are exactly determined by the stimulus amplitude. Accordingly, the relation between the number of autonomous progressions (Counts) and the stimulation amplitude ($\max S_{Stim}$) is given by a step function (Figure 3c, triangles and dashed line).

In contrast, with addition of noise, the resulting behavior can no longer be exactly predicted from the stimulus amplitudes because noise acts in a two-fold way (Figure 3b): first, noise induces event generation and, by that, leads to sensitization at previously uneffective stimulation levels (Figure 3b, $\max S_{Stim} = 23$, upper trace). Second, the noise can also induce transitions from event generation to subthreshold activity and therefore can suppress sensitization at previously effective stimulation levels (Figure 3b, $\max S_{Stim} = 25$, lower trace). The corresponding response curve ($D = 0.05$ in all cases) then becomes a probabilistic sigmoidal relation where, on average, sensitization is enhanced at low levels of S_{Stim} but suppressed at higher values of S_{Stim} (Figure 3c). Figure 3d summarizes the difference between the deterministic and the noisy behaviors, given as $\Delta\text{Counts} = C_{noi} - C_{det}$, emphasizing the two different effects of the noise on the sensitization process.

Minimizing Sensitization by Tuning of the Noise Intensity

The finding that noise can suppress the development of sensitization in the case of suprathreshold stimulation suggests that, on average, sensitization development could be minimized by tuning the noise intensity to an optimal level. Indeed this effect can be demonstrated on hand of the simulations shown in Figure 4. Using a suprathreshold stimulus level ($\max S_{Stim} = 25$), we get sensitization and autonomous progression under deterministic conditions (Figure 4a, $D = 0$, most upper trace). Adding a small amount of noise is sufficient to suppress sensitization development (Figure 4a, $D = 0.03$, middle trace). However, increasing the noise intensity (Figure 4a, $D = 0.5$, lower trace) again enhances the probability for event generation and, at high noise intensities, event generation occurs without any correlation to the trigger stimulus. Accordingly, the probability for autonomous progression then increases again. It is the compromise between noise-dependent suppression and induction of event generation, and the resulting autonomous progressions which leads to the *nonmonotonic* response curve shown in Figure 4b (counts of progressions *vs* noise intensity D).

DISCUSSION

In this paper, we examined how stochastic influences affect the initiation of episode sensitization in a computational model. We considered two different situations for sensitization development: (i) subthreshold activation of the model ('silent rest' without noise) and (ii) suprathreshold activation of the model (autonomous progression under deterministic conditions). Computer simulations were performed to systematically determine the noise effects on the sensitization behavior. Our findings demonstrate that noise has both enhancing and suppressing effects depending on the activity state of the model as well as on the respective noise intensity.

Our study was motivated by the argument that natural systems not only are mostly nonlinear but also always are subjected to random external and internal fluctuations. For example, human beings are subjected to various and variable forms of life stress, which can be approximated as a complex 'noisy environment' interacting with the human organism (Glassner and Haldipur, 1983; Kennedy *et al*, 1983; Bidzinska, 1984; Ambelas, 1987; Swann *et al*, 1990; Charney *et al*, 1993; Castine *et al*, 1998). In addition, biological systems—and brains in particular—themselves are intrinsically noisy. Neurons in the brain are subjected to various noise sources such as, among others, membrane potential fluctuations, synaptic noise, or random background activity. Moreover, noise sources cannot be assumed as constant as they might change because of altered neuronal function associated with different disease states or possibly as a result of psychopharmacological interventions (Ehlers *et al*, 1998; Huber *et al*, 1998).

Moreover, a magnitude of studies—reaching from the molecular up to the behavioral level—showed that noise cannot be simply regarded as a nuisance but can qualitatively change the behavior of a given system (eg Bezrukov and Vodyanoy, 1995; Astumian *et al*, 1997; Douglass *et al*, 1993; Braun *et al*, 1994; White *et al*, 1998; Gluckman *et al*, 1996; Rudolph and Destexhe, 2001; Simonotto *et al*, 1997; Winterer *et al*, 1999; Russell *et al*, 1999). Within the context of sensitization, such dynamic noise effects might have a long-lasting influence as they could induce long-term changes in the neurobiology of a respective organism and might even play a role for the progression of a mental disease such as recurrent affective disorder.

Our findings aggree with the SR literature and demonstrate interesting effects which, to the best of our knowledge, have not been considered so far with respect to models of sensitization dynamics. As already mentioned, the central point is the two-fold—enhancing as well as suppressing—action of the noise observed in the simulations. Noise enhances the probability of event generation and subsequent sensitization in the case of *sub*threshold activation. In this situation, noise amplifies existing instabilities of the model, which leads to oscillatory responses, event generation, and finally autonomous progression. This effect is related to SR and is in line with the noise-mediated detection of a weak, otherwise subthreshold, stimulus (Wiesenfeld and Moss, 1995; Bulsara and Gammaitoni, 1996; Gammaitoni *et al*, 1998). Being beneficial for neuronal signal encoding, this effect becomes a pitfall under pathophysiological conditions, in particular when it induces sensitization development as in our simulations (for a discussion of SR as a possible pathophysiological mechanism in neuroendocrine regulatory systems, see also Huber *et al*, 1999).

In contrast, noise reduces event generation and thus the probability for sensitization in the case of suprathreshold activation. The reason is that noise now induces transitions in the opposite direction—from event generating states to subthreshold states—and thus counteracts sensitization development. However, suppression of sensitization does not simply increase with increasing noise intensity. Instead, the relation now is nonmonotonic with the minimum of successful sensitizations at intermediate noise intensities. Qualitatively, this phenomenon is good to understand. With no or too little noise, the suprathreshold stimulus will always initiate event generation and subsequent sensitization. On the other hand, too much noise strongly enhances the probability for event generation even in the absence of the suprathreshold stimulus. In between the two extremes, a range of noise intensities exists where, on average, event generation is reduced. The conflicting roles of noise—enhancement and suppression—then result in the observed minimum curve for sensitization development. Therefore, under pathophysiological conditions, this effect might be beneficial as it could help a respective system to escape undesirable sensitizing feedback loops.

Our study shows that naturally occurring random fluctuations might have profound influences on sensitization behaviors. We note in passing that even more complicated behaviors can be expected when time dependencies of stochastic influences are considered (ie time-correlated colored noise instead of white noise, which also comes closer to the biological situation; see eg Fox *et al*, 1988; Longtin, 1997). Regarding the hypothesized role of sensitization mechanisms for the course of affective disorders, the recent nonlinear approaches to these disorders (Post and Weiss, 1995; George *et al*, 2001; Kramlinger and Post, 1996; Gottschalk *et al*, 1995; see also the pioneering work by Mandell *et al*, 1985) as well as the literature on dynamic stochastic effects in diverse neurobiological preparations, the consideration of stochastic-deterministic interactions is certainly of issue. In this sense, our findings contribute to the arising conceptual framework for understanding recurrence and progression in recurrent affective disorders. Apart from contributing to psychiatric thought, the described findings are of relevance for the understanding of sensitization mechanisms at the neurobiological level. Hence, it will be interesting to see whether the described principles do apply to kindling and sensitization in experimental preparations. Experimental evidences already exist, which demonstrate that the drug ethanol acts by introducing randomness or 'noise' in neuronal processing (Ehlers *et al*, 1998) and, speculation so far, such pharmacologically altered neuronal noise sources could also effectively interact with neuronal sensitization processes. This example further indicates the need to understand noise-mediated behaviors in neurobiology not only with respect to normal brain function but in particular regarding pathophysiological and clinical consequences.

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