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Chaotic behavior in dopamine neurodynamics

(schizophrenia/chaos)

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ABSTRACT **We report the results of the dynamics of a model of the central dopaminergic neuronal system. In particular, for certain values of a parameter $\bar{k}$, which monitors the efficacy of dopamine at the postsynaptic receptor, chaotic solutions of the dynamical equations appear—a prediction that correlates with the observed increased variability in behavior among schizophrenics, the rapid fluctuations in motor activity among Parkinsonian patients treated chronically with L-dopa, and the lability of mood in some patients with an affective disorder. Moreover our hypothesis offers specific results concerning the appearance or disappearance of erratic solutions as a function of $\bar{k}$ and the external input to the dopamine neuronal system.**

The dopamine hypothesis of the schizophreniform psychoses postulates an excessive central dopaminergic activity as the cause of certain symptoms of those diseases: hallucinations, labile and inappropriate affect, ambivalence, and disordered thinking (1–3). The support for such a hypothesis derives from several clinical findings. Amphetamine, a dopamine-releasing agent, can cause a paranoid psychosis in humans (4); antipsychotic drugs bind to central dopamine receptors with affinities that correlate well with their clinical potencies (5); and postmortem studies of the brain tissue of chronic schizophrenics find an increased receptor binding for neuroleptics (6). However, most studies show little difference between normals and schizophrenics in their mean values of parameters measured. Instead, in the schizophrenic pool, there is usually a significantly larger intersubject and intrasubject variance than among controls, an observation that has eluded explanation (7–9). This finding suggests that a more sophisticated model of dopamine dynamics may be appropriate for the understanding of psychotic behavior.

Until recently there have been few analytical studies detailing the complicated interactions between neuronal feedback and neurotransmitter kinetics that underly central monoamine neuronal systems (10). For dopamine, in particular, there appear to be mechanisms for local dendrodendritic inhibitory feedback and for long-loop striatonigral feedback from the caudate nucleus. Such feedback loops also are present in mesolimbic dopamine neurons (11, 12). Electrical stimulation of the nigrostriatal tracts results in an increased dopamine synthesis in the dopaminergic nerve terminals. Paradoxically, inhibition of dopamine firing also increases the synthesis of dopamine in the nerve terminals. This activation of synthesis at low firing rates is not found in the nigral dopamine dendrites or in other monoamine neurons (13). As demonstrated (14), this U-shaped curve of firing rate vs. dopamine synthesis predicts a bifurcation of stability in dopaminergic activity. For increasing activation of dopamine synthesis or with an increased amount or efficacy of dopamine at the postsynaptic receptors, a single stable equilibrium of dopamine firing can bifurcate into an unstable equilibrium and two stable equilibria, one firing slowly and the other firing more rapidly. In this report, we extend our analysis to the dynamic properties of such a dopamine system, taking into account the delay in dopamine synthesis activation and deactivation after a change in firing rate. We also state the main results of a global analysis of these dynamical equations, in particular, for certain values of a parameter $\bar{k}$, which monitors the efficacy of dopamine at the postsynaptic receptor, chaotic solutions of the dynamical equations appear that correlate well with the observed increased variability among schizophrenics. Moreover, our theory offers specific predictions concerning the appearance or disappearance of erratic solutions as a function of k and the external input to the dopamine neuronal system.

MATHEMATICAL ANALYSIS AND SIMULATION

The general equations that determine the nigrostriatal dopamine dynamics are given by:

$$\begin{aligned} \dot{x} &= \delta - x - \beta_1 y_1 - \beta_2 y_2 \\ \dot{y}_1 &= \alpha M x - \rho y_1 \\ \dot{y}_2 &= T x - \rho y_2 \\ \dot{M} &= \bar{\phi}(x) - dM, \end{aligned} \qquad [1]$$

where dots over letters denote time derivatives and symbols have the following meanings: δ, external depolarizing input to the substantia nigra dopamine cells; β_1, long-loop striatonigral feedback constant (proportional to the postsynaptic receptor number); β_2, short-loop nigral dendrodendritic feedback constant (proportional to the presynaptic receptor number); ρ, reuptake rate of dopamine [$t_{1/2} \approx 0.5$ min (15)]; T, nigral dopamine released per impulse; α, variable proportional to the release rate and the equilibrium constant for the synaptic stores of dopamine; d, degradative turnover rate of functional dopamine in the synaptic stores [$t_{1/2} \approx 4$–9 min (16, 17)]; x, firing rate of the dopamine neuron; y_1, postsynaptic concentration of striatal released dopamine; y_2, nigral concentration of released dopamine; M, concentration of dopamine in the functional synaptic stores; and $\bar{\phi}(x)$, striatal synthesis of dopamine as a function of the firing rate. We have illustrated the anatomical relationships among certain of these variables in Fig. 1. To study Eqs. **1**, we approximate the U-shaped form of $\bar{\phi}(x)$ (Fig. 2 *Left*) by

$$\begin{aligned} \bar{\phi}(x) &= A + B(x - \bar{x})^2 \quad \text{if } x < 2\bar{x}, \\ &= A + B \quad \text{if } x > 2\bar{x}. \end{aligned} \qquad [2]$$

We first notice that the reuptake rate of dopamine, ρ, and the relaxation of the firing rate of the dopamine neuron, x, are much faster than d, the degradative turnover rate of functional dopamine. This implies in turn that in the time evolution of x, y_1, and y_2 enter through their equilibrium values (i.e., $\dot{x} \approx \dot{y}_1 \approx \dot{y}_2 \approx 0$). In addition, experimental evidence suggests that there are substantial delays ($\approx$20–30 min) in the activation and deactivation of dopamine synthesis after changes in dopamine impulse flow (13, 18, 19). This allows

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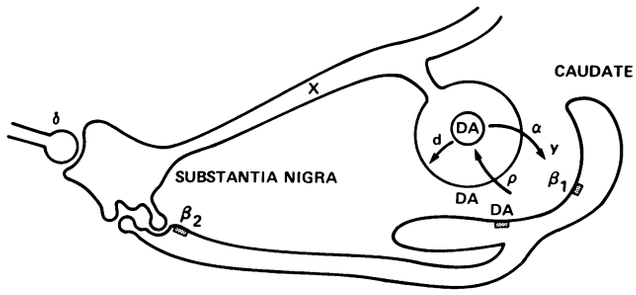

FIG. 1. A schematic representation of the anatomy and physiological processes depicted in Eqs. **1**. Included are mechanisms of dopamine release, reuptake, synthesis, degradation, and long-loop and local neurophysiological feedback.

us to rewrite the equation for M as a differential delay equation:

$$\dot{M}(t) = \bar{\phi}\{x[M(t - \gamma)]\} - dM(t). \quad [3]$$

Using an approximation scheme suggested by May (20), because $d_\gamma \approx 2$–6 we set $\dot{M} \approx 0$ and study instead the resulting nonlinear difference equation:

$$M_{n+1} = \frac{\bar{\phi}(x[M_n])}{d}. \quad [4]$$

After one substitutes for $x_n = x(M_n)$ the values obtained from Eqs. **1**, Eq. **4** simplifies to the following map schematized in Fig. 2 *Right*:

$$\hat{x}_{n+1} = \frac{\bar{\delta}}{1 + \bar{k}(\hat{x}_n - 1)^2} \quad \text{if } \hat{x}_n < 2$$
$$= \frac{\bar{\delta}}{1 + \bar{k}} \quad \text{if } \hat{x}_n > 2, \quad [5]$$

where

$$\bar{\delta} = \frac{\hat{\delta}}{1 + Q + s},$$

$$\bar{k} = \frac{s\psi}{1 + Q + s},$$

$$\hat{\delta} = \frac{\delta}{\bar{x}}; \hat{x} = \frac{x}{\bar{x}}; \psi = \frac{B\bar{x}^2}{A}; Q = \frac{T\beta_2}{\rho}; s = \frac{\beta_1 \alpha A}{\rho d}.$$

We numerically simulated the dynamics of Eq. **5**. It exhibits, for increasing $\bar{k}$, multiple bifurcations and chaotic solutions similar to those of the logistics equation (21, 22). We illustrated the full bifurcation diagram in Fig. 3. For $(\bar{\delta}, \bar{k})$ approaching the chaotic regime, the solution x_n will bifurcate progressively into periodic solutions of longer and longer periods (powers of 2 times the base period of 20–30 min). Finally for $(\bar{\delta}, \bar{k})$ within the chaotic domain, the solutions will demonstrate chaotic behavior characterized by broad band noise in the power spectral response, no discernible strict periodicity, rapid decay of correlations, and sensitive dependence on the initial conditions. Thus, dopamine activity will wander erratically over intervals of approximately 20 min. In addition, Eq. **5** produced the "cusp catastrophe" for the parameters illustrated in Fig. 3. This corresponds to the multiple equilibrium states discussed in ref. 14 and allows for the simultaneous existence of two stable states and attracting domains of influence. It should be added that the addition of other degrees of freedom in the form of external random fluctuations to Eq. **5** does not alter the general transition to chaos that we have outlined (23). Furthermore, a numerical simulation of the full differential delay Eq. **3** yielded a qualitatively similar, subharmonic period-doubling series of bifurcations to chaos. The coupling of two or more such "chaotic" oscillators has been shown to lead to not only a temporal but also a spatial disorganization of activity (24).

Recently, the values of the parameters entering our equations were estimated experimentally. Use of the concentration of dopa in the caudate as an index of synthesis of dopamine in the rat nigrostriatal system for various firing rates yielded the following values of parameters for this model as suggested by Miller (J. D. Miller, personal communication): $\bar{x}$, 3.8 Hz; x (normal), 4.7 Hz; x (kainic acid lesion of the striatum), 6.4 Hz (25); x (haloperidol), 7.8 Hz; A, 1 μg/g of dopa; B, 0.24 μg/g of dopa per Hz^2; Q, 0.188; s, 0.35; $\hat{\delta}$, 2; ψ, 3.46; $\bar{\delta}$, 1.3; and $\bar{k}$, 0.8. We have illustrated (Fig. 4) the temporal dynamics of Eq. **5** for these parameters and the effect of increasing s, decreasing Q to 0, and increasing δ, through, for instance, the addition of amphetamine to increase α (dopamine release) under simultaneous external activation of firing.

DISCUSSION

These results lead to several interesting clinical predictions. First, the erratic behavior in dopamine dynamics will produce a large rise in the variance of any parameter monitoring the central dopamine activity, thus providing a possible ex-

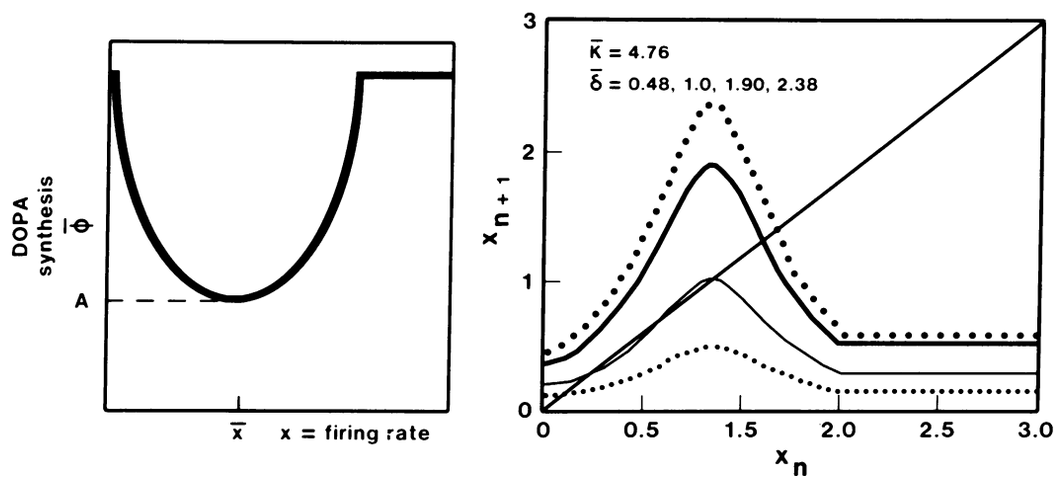

FIG. 2. (*Left*) Dopamine synthesis $\bar{\phi}$ vs. firing rate x; notice the U-shaped behavior of the curve. (*Right*) The resulting iterative map $x_{n+1} = f(x_n)$. $\bar{x}$ has been normalized to 1. For increasing $\bar{\delta}$, the plotted curves have increasing maxima. Notice that for $\bar{\delta} = 1$, there are three intersections with the curve $x_{n+1} = x_n$. This gives rise to the multiple equilibrium states (MES) described in the text.

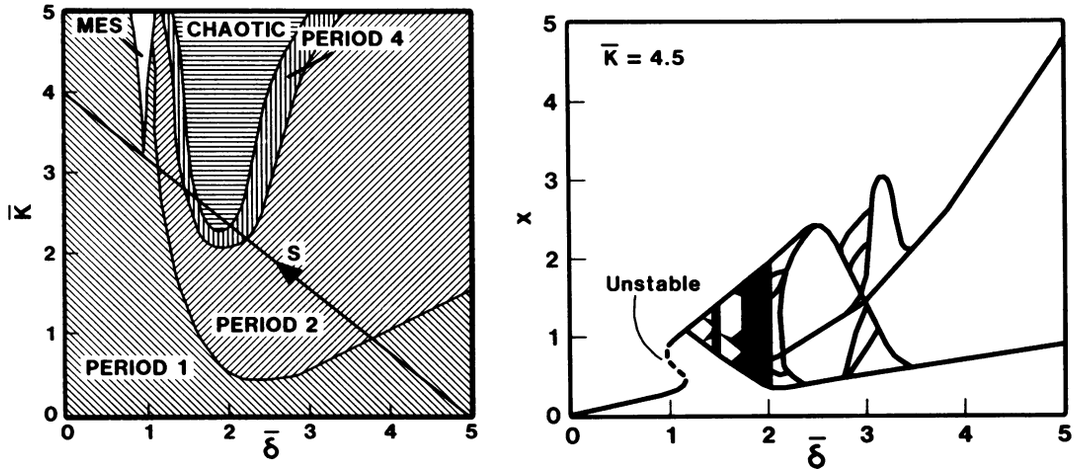

FIG. 3. (*Left*) Bifurcation diagram showing the dynamic behavior of the dopamine system as a function of $\bar{k}$—a measure of the synthesis, effectiveness, and availability of dopamine at the postsynaptic region—and of $\bar{\delta}$, the normalized depolarizing input for the dopamine neurons in the substantia nigra. Notice that for a fixed input $\bar{\delta}$, increasing s—a measure of the efficacy of dopamine at the synapse—can lead to a progressive change in behavior from monostability to chaos. Increasing s further will lead to the reverse sequence of behavior and can result in an eventual monostability. (*Right*) A cross section of *Left* schematizing the dynamics of Eq. **5** for various $\bar{\delta}$ with $\bar{k}$ = 4.5. x is the firing rate in units of $\bar{x}$. For increasing $\bar{\delta}$, the system first bifurcates into a bistable state and then continues to bifurcate in a manner similar to the logistics equation into chaotic solutions, here denoted by the solid blocks.

planation for the reported fluctuations in mood, attention, and activity in schizophrenics (7–9, 26). Also it has been reported that after chronic L-dopa treatment of Parkinson's disease, many patients will randomly shift from a hyperkinetic to an akinetic state and vice versa over a period of minutes, a behavior termed the "On-Off Phenomenon" (27, 28). Because L-dopa is readily synthesized into dopamine and may cause long-term changes in receptor sensitivity, one could envision driving the system chaotic by increasing $\bar{k}$, thereby observing such behavior. The parameter $\bar{k}$ is sensitive to changes in Q, which in turn depends linearly upon β_2, a measure of nigral autoreceptor activity. Thus, by decreasing presynaptic receptor activity and thereby increasing $\bar{k}$, one could also trigger chaotic behavior. Because chronic treatment with tricyclic antidepressants, amphetamine, or rapid-eye-movement sleep deprivation appears to cause a hyposensitivity of the nigral dopamine autoreceptors (29, 30), these procedures could all result in the sudden appearance of this erratic dopamine activity. In addition, the parameter $\bar{k}$ is also susceptible to changes in s, so that increasing s through acute-dose amphetamine ($\uparrow \alpha$-$\uparrow$ release of dopamine), or high-dose apomorphine ($\uparrow \beta_1$-activation of postsynaptic receptors) could produce or increase the randomly fluctuating activity. Likewise, decreasing s by adding reserpine ($\downarrow \alpha$-$\downarrow$ synaptic stores of dopamine), α-methyl-*p*-tyrosine ($\downarrow A$-$\downarrow$ dopamine synthesis) or neuroleptics ($\downarrow \beta_1$-blockade of postsynaptic receptors) could reverse this characteristic chaos. Finally, the model may explain the anomalous observation that in certain schizophrenics, acute amphetamine may actually improve their psychotic symptomatology (31). This could be achieved through an *increase* in s, with constant δ, forcing the system to pass through the chaotic regime (see Fig. 3).

Although this model predicts that psychotic individuals may manifest rapid variations in affective and motor behavior; it is important to link a postulated dopaminergic instability to the rather rigid and idiosyncratic delusional thought content shown by many schizophrenics. A heightened dopamine activity has been associated with reward-seeking behavior in a variety of paradigms (32). One could hypothesize that schizophrenics experience unpredictable, endogenously generated fluctuations in reward seeking correlated with the proposed chaotic fluctuations in dopamine activity. Skinner (33) originally noted that pigeons, when intermittently rewarded with food independent of their ongoing behavior, rapidly develop stereotyped motor activity that is slow to extinguish. He termed this process "superstitious conditioning." These experiments have been replicated in other species and with a variety of forms of noncontingent reinforcement (34). One could speculate that because of "random"

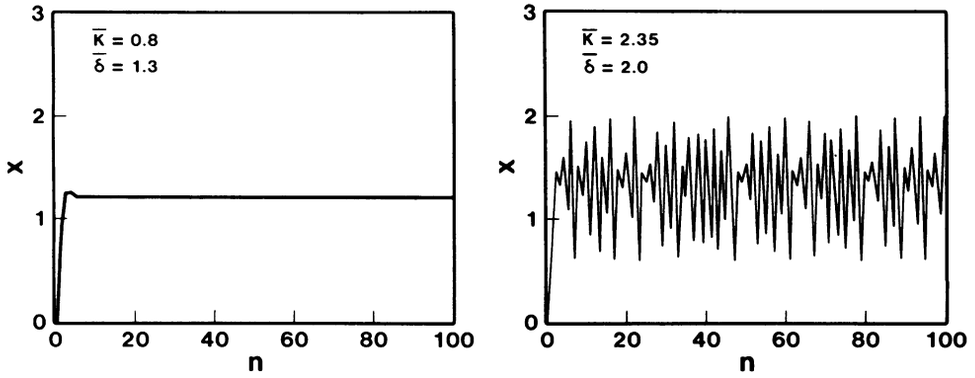

FIG. 4. Temporal dynamics of Eq. **5**. n is normalized to multiples of the base period y. (*Left*) $\bar{k}$ = 0.8 and $\bar{\delta}$ = 1.3 were chosen to best approximate the available experimental data. (*Right*) $\bar{k}$ = 2.35 and $\bar{\delta}$ = 2; here increasing s and $\bar{\delta}$ give a chaotic dynamics.

variations in dopamine activity, psychotics might construct elaborate, bizarre thoughts or actions in anticipation of future reward. This cognitive behavior could be quite persistent like that observed in the Skinner experiments. Thus, a disrupted temporal organization of dopamine activity *per se* might have profound effects on learned behavior.

Although the simulations presented here are based on the difference Eq. **4**, an der Heiden and Mackey (35) have recently demonstrated the occurrence of period-doubling chaotic bifurcations for differential delay equations that contain a single hump function governing the feedback of the underlying process, like that of Eq. **3**. Their proof is rather robust and offers further evidence that the full differential delay equation will give rise to chaotic solutions similar in form to the solutions of the difference equation modeled in this paper.

The theory proposed for dopamine dynamics is consistent with a wide variety of causes of psychotic behavior. Cronin (36) has offered a general model of periodic catatonia based upon an instability in thyroid function. The model presented here, however, is very specific and thus amenable to experimental testing. Increased activation of dopamine synthesis, supersensitive postsynaptic dopamine receptors, hyposensitive presynaptic receptors, or a disturbance in another neurotransmitter system (neuropeptides, serotonin) that impinges upon and influences dopamine activity, could all lead to a similar ultimate fate: erratic dopamine dysfunction.

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