Chaos and Schizophrenia: Does the Method Fit the Madness?

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Over the past 30 years, investigators have used nonlinear and so-called chaos theory–based techniques to examine a wide range of phenomena ranging from electroencephalogram and cardiac rate and rhythm analyses to stock market and weather predictions. Psychiatric neuroscientists are now beginning to apply nonlinear methods to mental disorders such as schizophrenia. These applications are relevant from the level of complex genetic architecture and calcium channel dynamics to the symptomatic, behavioral, and functional outcome of schizophrenia. The key point of this surge of interest is distinguishing complex, nonlinear but lawfully mediated systems from truly random systems. The application of these methods to studies in schizophrenia has yielded findings that are consistent with the general hypothesis that an altered sequential or temporal architecture is a key feature of this disorder. Specifically, we propose that the temporal architecture of schizophrenia is characterized by bursts of complex, nonlinear phenomena alternating with truly random events. Analyzing these patterns of molecular (e.g., calcium channel activity) to molar (e.g., symptom level) phenomena via nonlinear systems methods can provide new approaches to understanding complex temporal and sequential shifts in neural substrate activity, pathophysiology, and the course and treatment and outcome of schizophrenia. Biol Psychiatry 2003;53: 3–11 *© 2003 Society of Biological Psychiatry*

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Introduction

Over the past three decades, studies of nonlinear systems have revealed remarkable new insights into how to characterize and study the manner in which biological and physical systems evolve over time (Braiman et al 1995; Eckmann and Ruelle 1985; Lorenz 1958; May 1987; Rossler and Rossler 1994). Among these insights is the finding that random-appearing series of events across time (see Table 1 and Figures 1 and 2) can be generated by surprisingly simple underlying rule-based systems (Feigenbaum et al 1982; Mayer-Kress 1986). For example, the random-appearing sequential flight pattern of an Albatross is actually characterized by a lawful pattern that depends on the Earth's geometry and the bird's fundamental drive to forage for food (Stanley et al 1996). The mathematical characteristics of this type of sequential pattern occurs in a wide range of systems (Shlesinger et al 1987) including heartbeat variability (Peng et al 1993), DNA coding sequences (Ossadnik et al 1994) and, even at the "macro" level, the information flow in large companies (Mantegna and Stanley 1997) and in abstract neuronal models (Mandell and Selz 1997). This striking relationship of simple underlying systems leading to random-appearing phenomena has important and well-documented implications for the study of mathematical, theoretical, and physical systems (Ruelle 1994). The methods and techniques that have been developed in these nonlinear approaches are now being applied to many biological and neurobiological systems (Glass and Kaplan 1993; Mandell 1983), including understanding neuropsychiatric phenomena such as schizophrenia (Havlin et al 1995) and affective disorders (Bengel et al 1998; Huber et al 2000; Moss 1994; Tschacher et al 1997).

The disturbances of associations (i.e., the perturbation of normal links between thoughts) are readily observed over time and were proposed by Bleuler as one of the key features of schizophrenia (Bleuler 1950). Given the complex and seemingly random pattern of thought and behavior of schizophrenia patients, it seems reasonable to inquire whether methods from nonlinear dynamics, which are aimed to quantify the evolution of nonlinear systems over time, may be useful in understanding schizophrenia. The compelling idea of nonlinearity and "chaos theory" (for definitions of terms, see Table 2) has its greatest face validity when applied to schizophrenia. In patients with this disorder, complex, dysregulated neurocognition, such as fixity on the Wisconsin Card Sorting Test (Braff et al 1991; Goldberg and Weinberger 1988; Perry et al 2001), is associated with other aspects of the patients' behavior and cognition that appears to be grossly nonfixed and disorganized (Cohen and Servan-Schreiber 1993; Hoffman 1987; Liddle and Morris 1991; Weinberger 1987). On multiple levels, from neural substrates to symptoms and

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Table 1. An Exemplary Time Series

Time	1	2	3	4	5	6	Statistics
Series 1	100	100	100	50	50	50	M = 75, SD = 27
Series 2	100	50	50	100	100	50	M = 75, SD = 27

See legend for Figure 1.

social behavior, events are organized in a complex appearing but rule-driven manner across time and across sequences of observations (Paulus 1997). A coherent temporal or sequential architecture emerges from the rules that define patterns of events across space and time (i.e., the order of behaviors and the relationship of "strings" of behaviors; cf. Figure 1). Nonlinear methods derived from chaos theory provide tools that allow us to quantify the temporal architecture and may help us to understand the disease process underlying schizophrenia (Paulus et al 1996) and other psychiatric disorders (Gottschalk et al 1995).

Inherent in nonlinear systems approaches is the assumption that, although a series of observations in time or space may appear complex, relatively simple underlying "generators" may drive these behaviors. Thus, the timing or sequential nature (or both) of these phenomena are based on quantifiable rules, as opposed to non-rule-based, random patterns of behavior. Initial studies have focused on testing whether a system is chaotic (i.e., exhibits complex but lawfully mediated behavior that is highly sensitive to small perturbations) or whether it is truly random (Babloyantz and Destexhe 1986; Goldberger 1991; Kaplan and Cohen 1990; Rapp et al 1994). Mathematically, nonlinear systems are characterized by the observation that the input is not necessarily proportional to the output, that is, increased input does not necessarily lead to a proportionally increased output. Chaotic dynamical systems are

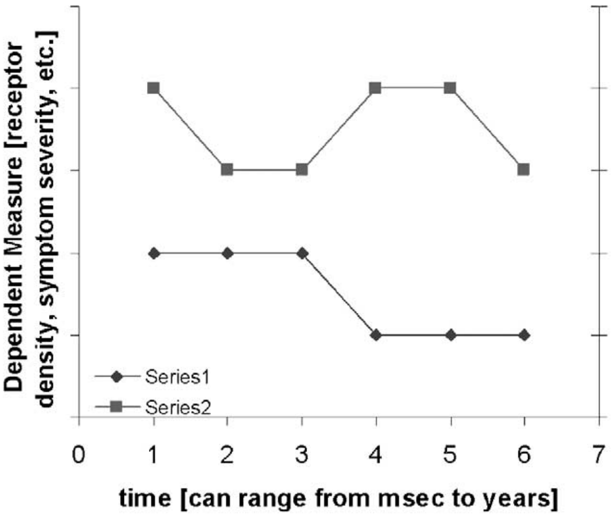

Figure 1. An exemplary time series of data that show the importance of temporal architecture; see also Table 1. The y axis represents arbitrary values that could correspond to neuronal channel kinetics or symptom fluctuations in neuropsychiatric patients and may vary in time from milliseconds to years. It is important to note that traditional statistical measures (see Table 1) that do not take into account the temporal characteristics of the measure are unable to quantify the profound differences between the two time series shown here and in Table 1.

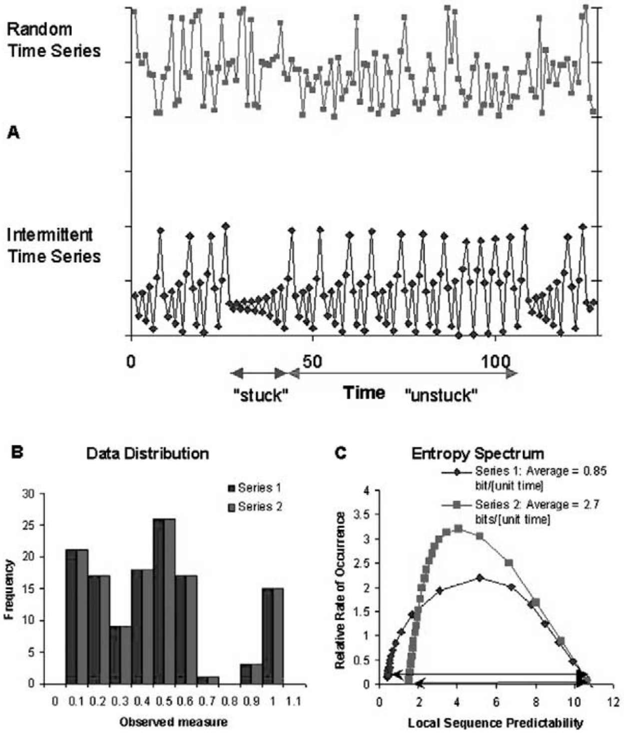

Figure 2. Two hypothetical time series of data points illustrate the concept of intermittency as one variant of temporal architecture that may be critical for schizophrenia. In panel A, the top series of data points illustrates a random (nonlawful) pattern. In contrast, the series of data points in panel B represents a complex but rule-driven series of data points in the temporal domain. Two regimes characterize the series of data points in panel B. First, some sequences that are confined to a small part of the available range of data points ("stuck"). Second, there are sequences of data points that cover the entire range of observations ("unstuck"). The episodes of "stuck" data points occur intermittently, that is, at irregular intervals separated by "unstuck" episodes. The actual distributions of both series of data points are shown in panel B. The mean, standard deviation, or any statistic that does not take into account the temporal architecture of the data are not able to distinguish the two series of data points. In comparison, the entropy spectrum shown in panel C significantly differentiates both series of data points. As reflected in panel C, the average entropy, a measure of randomness for the series of data points shown on top in panel A is more than three times higher than the average entropy for the series of data points shown on the bottom.

Table 2. Frequently Used Terms in Chaos Theory and Nonlinear Science

Term	Definition	Reference
Deterministic	A rule exists that relates input to output, past to present, an observation at one point in space or time to an observation at another point in space or time	(Haken 1978; Mayer-Kress 1986)
Random	Factors such as input, past behavior, or observations at one point in space or time do not provide valid predictive information about output, the present, or observations at another point in space or time	(Feller 1957)
Linear	Changes in input results in proportional changes to the output	
Nonlinear	Changes in input can result in seemingly "unpredictable" but rule-based large or small changes to the output	(Ruelle 1978)
Generator	A system that relates input to output, past to present, one point in space or time to another point in space or time in a lawful manner	(Crutchfield and McNamara 1987)
Trajectory	The sequence of observations in space and time	(Eckmann and Ruelle 1985)
Attractor	The coherent sequence of observations to which a system evolves over time	(Eckmann and Ruelle 1985)
Sensitivity to initial conditions	Two initial observations that differ by a small amount lead to strikingly different trajectories and "final states"	(Li and Yorke 1975)
Chaotic	A system with a trajectory that, while predictable and lawful, may appear random and is often characterized by extreme sensitivity to initial conditions	(Eckmann and Ruelle 1985)
Predictability	The degree to which the input, past, or observation at one point predicts the output, present, or observation at another point in space or time	(Grassberger 1989b)
Entropy	A measure of randomness	(Grassberger 1989a)
Intermittency	Coexistence of and mixing between multiple types of trajectories: 1) chaotic trajectories with low predictability (random trajectories with no rule-driven predictability) and 2) highly predictable trajectories	(Manneville 1980)

characterized by a lawful but exquisite sensitivity to initial conditions. This sensitivity to initial conditions leads to the observation that initially similar behaviors evolve into a striking divergence of behavioral patterns over time. Therefore, small differences in the input can result in an entirely different sequence of outputs. This altered input–output relationship is exemplified in schizophrenia by the finding that overstimulation or sensory overload (e.g., (Braff 1989; Gottschalk et al 1972) may be paradoxically associated with negative symptoms, fixity, or even catatonia.

The strict distinction between orderly versus random events, however, may prove to be a "straw man," because many biological systems demonstrate concurrent admixtures of both complex but rule-driven elements and random elements, which has been described as "constrained randomness" (Mandell 1986). Even more important, new dynamical features may emerge from the interaction between random fluctuations and underlying nonlinear dynamics. For example, noise, that is, random events that are not related to the system, can alter the inherent nonlinear dynamics of mood swings so as to shorten or lengthen the duration of illness (Huber et al 2000). Quantifying the longitudinal patterns of affective disorders, Huber et al (1999) noticed that random events may increase the spectrum of dynamic behaviors, enhance the responsiveness to weak activations, and facilitate the occurrence of nonperiodic patterns. Others have hypothesized that information-processing characteristics can be viewed within a nonlinear framework and have suggested that intoxication with alcohol introduces randomness in nonlinear constrained neuronal processing (Ehlers et al 1998). A variety of approaches are now available to examine the basic nonlinear deterministic "skeleton," which include methods such as detrended fluctuation analysis (Peng et al 1996), unstable period orbit analysis (Faure and Korn 1997), or noise reduction methods (Kantz and Schreiber 1998). The application of these methods enables one to quantify the degree to which nonlinear or chaotic mechanisms are at work in a complex sequence of observation in time or space.

Applications of Nonlinear Methods to Human Disorders

To use a prototypical example from cardiology, heart beat variability shows complex, nonlinear patterns that can be used to predict transition to arrhythmia and sudden cardiac death if even a modest electrical input occurs during a vulnerable period of cardiac depolarization (Goldberger

1990). At a more global level, measles epidemics follow predictable but random-appearing temporal patterns (Schaffer 1985; Sugihara et al 1990). These random-appearing phenomena including the secretion of parathyroid hormone (Prank et al 1994), neuronal firing patterns (Freeman 1994; Lopes et al 1994), and electroencephalographic (EEG) recordings (Babloyantz and Destexhe 1986; Roschke and Aldenhoff 1992) generate temporal signals that have been analyzed and successfully classified using nonlinear dynamical systems methods. Application of nonlinear analyses may also yield quantifiable phenotypes that could be related to underlying genetic phenomena. For example, lower EEG attractor dimension, a measure of nonlinear complexity, was found in alcohol-dependent subjects with positive family histories but not in their counterparts with negative family histories (Ehlers et al 1995).

These findings are consistent with the idea that carefully characterizing the temporal domain of the biological system at hand can lead to important insights into the function and dysfunction of the underlying biological substrates. In this conceptual framework, average measures quantifying brain–behavior relationships are important, but the sequence and timing of events yields distinct and crucial information for understanding these relationships (Table 1).

Why have nonlinear and chaos theory–based approaches not advanced the field of psychiatric neuroscience compared with other disciplines, such as cardiology (Goldberger 1991)? There are several answers to this question. First, the methods and techniques of nonlinear dynamics have been veiled in unfamiliar terminology and are based on advanced mathematical approaches that are likewise unfamiliar to many researchers in psychiatric neuroscience. Second, the approach taken by researchers in the field of nonlinear dynamics is to develop a quantitative framework for the mesoscopic view (i.e., a midlevel description) of a complex system (Haken 1996). This mesoscopic view is rooted in the idea that the behavioral pattern of a system can best be understood as an emerging property of highly interacting molecular or submolecular processes (e.g., the opening and closing of calcium channels in microcirculation [Griffith 1996]), which yields "macro" events that are visible on a larger temporal or spatial scale (heart attacks). At this point in time, the neuroscientific, genetic, and molecular biological revolution of the past decade has driven the focus of investigation of neuropsychiatric disorders into an increasingly molecular and submolecular scale. Using known molecular (micro)systems to construct models and evaluate larger scale behavior is now beginning to emerge in psychiatric neuroscience. Thus, large-scale processes (i.e., the observation of human interactive behavior over time) is now being quantified using advanced methods such as functional neuroimaging (Berns et al 1999; Dhamala et al 2002).

Third, some early findings using nonlinear methods have been related primarily to psychologic constructs in an impressionistic manner (Sabelli et al 1990) that did not result in the generation of falsifiable hypotheses that can lead to a progression of scientifically testable hypotheses and models (Platt 1964). Fourth, to reliably measure the flow of thought or emotion across time or in sequence is a daunting experimental challenge that requires the development of new approaches and tasks. Although simple behavioral tasks such as the two-choice prediction task (Paulus 1997) or the assessment of finger movements (Schoner and Kelso 1988) are providing a means to assess long strings of simple behaviors in a controlled context, they do not quantify thoughts and emotions with the precision that an electrocardiogram quantifies the electrodermal activity due to cardiac conduction changes.

Several important developments that strongly support the notion that chaos-based methods may lead to useful applications in psychiatric neuroscience. Mandell (1983, 1986) (Mandell and Selz 1995) and Freeman (1994) showed that the application of nonlinear dynamic systems methods produce exciting new insights into the fundamental mechanistic nature of neuropsychiatric disease processes. This approach focuses on the domain of "phase space," which comprises the range of values that a neuropsychiatric system can exhibit over relatively long periods of time (Gottschalk et al 1995). The sequential ordering of these values by an adaptive and healthy biological system is subject to the interaction with other variables. For example, nonlinear measures of EEG recordings (Roschke and Aldenhoff 1993; Stam et al 1994), sequences of behaviors (Paulus et al 1990, 1996), and fluctuations of psychiatric symptoms over time (Gottschalk et al 1995; Tschacher et al 1997) have been used to distinguish patients from normal comparison subjects (Roschke and Aldenhoff 1993). It appears, however, that the emerging nonlinear patterns in these data result from the interaction between the internal state of the system (i.e., the underlying neurobiology of the neuropsychiatric disorder) and external unpredictable (i.e., random) events. For example, environmental events that are not planned or predictable may significantly alter the inherent dynamics of affective disorders (Huber et al 1999, 2000). Alcohol may change how subjects process information from a nonlinear mode with few degrees of freedom to a random mode that is highly unpredictable (Ehlers et al 1998). In contrast, depression may change information processing as measured by EEG from a nonlinear mode to a highly constrained rigid set of information processing rules (Nandrino et al 1994). These results support the general hypothesis that the temporal and sequential dynamics of psychiatric phenomena are due to the interaction between the organizational state of the neurobiological system and external perturbations. Nevertheless, the quantification of specific relationships between, for example, psychiatric symptoms during the course of affective disorders and external random events awaits further systematic study.

Experiments in Schizophrenia

Our series of studies examining behavioral sequences of schizophrenia patients support the general hypothesis of an altered temporal architecture of behavior such that healthy (flexible) behavior and unhealthy (fixed) behaviors coexist in the same patient at the same time (Paulus et al 1994, 1996, 1999a, 1999b, 2001). Specifically, to obtain a methodologically viable behavioral time series of many individual observations and to examine this time series using nonlinear dynamical systems methods, we asked subjects to predict whether a randomly presented stimulus would appear on the left or right on a computer display. These "choice task" studies have been conducted for many years in psychology and psychiatry (Dale 1966; Frith and Done 1983; Lyon et al 1986) to understand the underlying sequential structure of self-generated behavioral patterns. These studies have shown that normal volunteers show complex behavioral patterns that are neither completely random nor completely fixed and deterministic (Dale 1966). Using a simple left–right two-choice task, we observed that normal subjects generate sequences of behavior that are influenced significantly by previous behavior and stimuli. This orderly relationship occurs even though correct choices are not related at all to the subject's "choice strategy." Thus, we can assess the influence of a subject's "prediction history" on their ongoing left or right choices. In comparison to normal subjects, schizophrenia patients show an altered sequential architecture of their choice-task behavior. Specifically, schizophrenia patients generate sequences of choices that are highly predictable, but during the same test session these patients also generate sequences that are highly unpredictable.

This schizophrenia-linked pattern of "intermittency" of fixed and random choice sequences can be characterized using a number of approaches. For example, one can quantify "sequence predictability" by the degree to which each behavioral sequence can be predicted based on all other behavioral sequences generated by the subject. As a group, the range of this predictability of choices is significantly larger for schizophrenia patients relative to normal comparison subjects. At the same time, there is a coexistence of highly predictable and highly unpredictable sequences within the behavioral pattern of an individual schizophrenia patient. This intermittency pattern points toward a fundamental alteration of sequential patterning of behavior in schizophrenia patients. These choice task results in schizophrenia patients raise a number of important questions. 1) Is this behavior pattern stable across time? 2) Is a high degree of intermittent behavior during the choice task specific to schizophrenia? 3) Is the behavioral pattern of intermittent fixed and random bursts or choices related to other dysfunctions in schizophrenia patients (e.g., symptoms, neuropsychologic functions)? 4) Can these patterns of fluctuating fixed and random choices be used to predict treatment response? 5) Can the schizophrenia patients' behavioral patterns be related to the functional status of patients? 6) How can we best relate the neural substrate abnormalities in schizophrenia patients to the "signature" of fixed and random admixtures of abnormal behavior? We have begun to address a number of these questions in a series of studies. The main conclusion from these studies is that the pattern of the time series of behavioral data obtained from schizophrenia patients can be observed during the patient's first psychotic episode, is independent of medication status, is stable across time, and may affect only a significant but discrete subset of schizophrenia patients. In addition, in a brain-imaging paradigm, this abnormal intermittency of fixed and random bursts of self-generated behavior is related to the activation of prefrontal–parietal cortex (Paulus et al 2002).

Supporting our conclusions, other investigators have found similar changes in sequential or temporal architecture in the clinical course of schizophrenia symptoms. For example, Tschacher and colleagues (Tschacher 1996; Tschacher et al 1997) report intermittent changes in positive and negative symptom status resulting in long-range correlations of symptom profiles across time. The existence of long-range correlations is consistent with a complex organization of temporal behavior and is frequently found in systems with coexisting stable states (Grassberger 1986). Based on these behavioral findings, we suggest that the dysfunction in schizophrenia patients may be productively analyzed in the temporal or sequential domain. If one assumes that continued information and cognitive processing is crucial to appropriately adapt to a complex environment and that intermittent information and cognitive processing deficits are central to schizophrenia patients, one can begin to derive a number of predictions. First, the sequential and time series of intermittent systems when collapsed across the temporal domain are highly variable (i.e., generate large standard deviations). Second, intermittent systems are highly sensitive to perturbations (i.e., small changes that affect the system can result in large changes of the temporal architecture). Third, these systems give rise to complex temporal correlations (i.e., an event that may have occurred a long time ago may still have a significant effect on the current state). These three properties of intermittent systems lead to specific hypotheses of behavioral and neurobiological time series obtained from schizophrenia patients: 1) high intrasubject variability, 2) sensitivity of the time series to small external perturbations, and 3) the existence of long-range correlations.

Novel Applications

Unquestionably, the signs, symptoms, and even diagnoses of psychiatric patients change in a complex pattern over time. Yet most investigations that examine changes of behaviors and symptoms longitudinally limit themselves to descriptions of improvement or deterioration using a variety of simple statistical approaches that may fail to capture the complexity of the symptom or function outcomes being studied (Fleiss 1981). Therefore, a number of fundamental questions remain unanswered about the time course of symptoms in serious neuropsychiatric disorders such as schizophrenia. First, what are the precise characteristics of the temporal or sequential architecture that characterizes psychiatric signs and symptoms? Second, do treatments alter the temporal or sequential architecture of signs and symptoms? Third, can the temporal evolution of signs and symptoms be quantified and classified into different categories? Fourth, can one link various temporal evolutions of signs and symptoms to underlying pathophysiologic processes or the complex architecture of genetic subtypes?

Addressing these four questions now appears to be possible, although the translation of these questions into testable and falsifiable hypotheses is challenging. There are several important issues that need to be addressed when considering the application of nonlinear dynamic systems methods to data generated in neuropsychiatry. As opposed to many physical systems (e.g., forced Rayleigh–Benard system [Jensen et al 1985] or mathematical systems [Li and Yorke 1975]) that can be observed indefinitely and can be put into a long-range temporal context that renders them relatively unchanged over a long period of time, biological events are often inherently nonstationary. This ever-changing situation is similar to observing fluctuations in serial observations of the weather or stock market. Several statistical approaches from other disciplines have been developed to address this issue of scaling in the temporal or spatial domain (Mantegna and Stanley 1997). The observation of signs and symptoms poses serious temporal and reliability challenges: it makes no sense and is not possible to subdivide the severity of a symptom into too many levels or to measure psychiatric symptoms on a second-to-second basis, as can be done with EEG data. Nevertheless, methods from symbolic dynamics (Crutchfield and Packard 1982; Hao 1991), an approach that is used to transfer a dynamic system into one that exists in a few clearly distinguishable states, may help to address this problem by separating the dynamical system into few clearly definable states.

The signal-to-noise ratio of many psychiatric neuroscience time series is orders of magnitude lower than that of physical systems that have been studied using nonlinear dynamic systems methods. Some investigators have developed noise-reduction methods (Schreiber 1993); other methodologists have generated “noisy time series” methods to model various processes and to compare temporal parameters across systems to test hypotheses about the comparison of time series across time epochs and types of data (Theiler 1994). In psychiatry and other fields of medicine, it is of great importance not “just” to observe the evolution of events of interest across time, that is, the natural history of a disorder. We also aim to modify the events, that is, treat the disorder. There is a window of opportunity during which one is able, indeed may be required, to investigate the temporal course of the untreated disease process before ethically mandated treatment is started; however, it is unclear whether a short window of observation of the sequence and time course of a disease process, for example, the fluctuation of symptoms in schizophrenia or bipolar disorder, is sufficient to generate meaningful predictions about the long-term outcome of the disorder. In addition, can a relatively short time frame inform us about our “success” in modifying this process using treatments? These are important questions that lie before us using nonlinear conceptual frameworks and methods.

Conclusions

In summary, the study of nonlinear dynamic systems has generated enormous interest across a wide range of scientific fields, from weather predictions microcirculatory events, heart rate and rhythm analysis, hormone secretions, and EEG dynamics, to neuropsychiatric symptom fluctuations. Recent studies, particularly in the medical sciences, have been enticing, but the application of lawful nonlinear methods has just begun to lead to important new insights into the underlying disease process and treatment of disorders, such as cardiac electrical abnormalities (Goldberger 1990). The work that lies ahead is to connect these “dynamic” insights to the assessment and prediction of the functional status and treatment response of patients with various mental disorders. Moreover, it is critical to determine which pharmacologic and psychosocial interventions have a predictable impact on the temporal course of neuropsychiatric disorders (e.g., assessing the effects of medications and cognitive–behavioral therapy). We need to assess how treatment effects on symptoms and neurocognitive functions can be predictably quantified using nonlinear dynamic systems methods. Finally, the findings in schizophrenia patients reviewed in this article (Paulus et al 1996, 1999a) can lead to a generation of new testable hypotheses that relate behavioral findings and neurophysiologic data to the neural substrate function underlying normal and abnormal behavior.

We hypothesize that one central component of dysfunction in the temporal or sequential domain in schizophrenia is the coexistence of lawfully driven fixity (high predictability) alternating with chaos (low predictability) in an intermittent fashion within the same subject, even during the same test session. In particular, the temporal intermittency observed on a behavioral level in schizophrenia patients may correspond to the intermittent activation patterns of neural systems and their underlying neuronal events (i.e., ion channel activity; Liebovitch and Todorov 1996). If this type of information were quantified, then one would predict that a key component of schizophrenia spectrum disorders is the characterization of how neural substrates function over time using nonlinear methods. For example, one could hypothesize that the disease process of schizophrenia is due to an alternating fixed and entropic flow of information in key neural substrates that process complex information. In this case, intermittency ultimately may be linked to factors such as a fundamental alteration of the membrane properties of neurons associated with the transmission of information across neuronal assemblies. This intermittency can disrupt normal information processing and result in the inability to recall important contextual information or lead to disorders of higher level cognitive functions, such as working-memory deficits (Perry et al 2001), gating disorders (Braff and Geyer 1990), or “cognitive dysmetria” (Andreasen 1999).

Thus, lawful chaos and nonlinear methods may form an optimal platform from which we can understand many aspects of schizophrenia. Then we can assess how treatment leads to the potential normalization of intermittency (i.e., a mixture of lawful and random events) on a basic and clinical level. From a preclinical science perspective, antipsychotic compounds could be screened based on their ability to correct drug-induced abnormal intermittency of neural circuit firing patterns. From a clinical science perspective, assessing the reduced intermittency of signs and symptoms may be one method of both understanding schizophrenia treatments and predicting longer term clinical efficacy. Thus, in terms of chaos theory and schizophrenia, the method does indeed appear to fit the madness and also offers many exciting opportunities to advance our understanding and treatment of this uniquely “nonlinear,” perplexing, and enigmatic group of disorders.

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