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Long-range correlations in choice sequences of schizophrenic patients

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Abstract

Schizophrenic patients significantly greater than normals exhibit long-range correlations in sequences of choices in a simple binary choice task. Moreover, schizophrenic patients also are significantly less influenced by external stimuli than are normal comparison subjects. These effects are not significantly correlated with each other, suggesting that they do not result from a uniform attentional deficit nor are they due to simple perseverative responding or any other uniform process. The interdependence of responses over many trials suggests that the response history of many previous behavioral responses contributes significantly to the temporal architecture of schizophrenic patients. In agreement with others (Lyon et al., 1994), we find that similar organizational principles apply to physical, economical, or biological systems and seem to play an important role in human psychopathology. © 1999 Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

Schizophrenia is a complex illness characterized by multiple types of symptoms involving many aspects of cognition and emotion (Andreasen, 1997). In particular, schizophrenic patients have prominent cognitive dysfunctions in attention and information processing (Braff, 1993), organization of thinking (McGrath, 1991), and sequencing of behavior (Paulus et al., 1996). These dysfunctions have been conceptualized as resulting from abnormal distractibility (Grillon et al., 1990), deficient gating (Braff et al., 1995), dysfunctional behavioral organization (Paulus et al., 1996) and impaired neuro-anatomical ‘connectivity’ (Liddle, 1996). The focus of this study is to elucidate how these cognitive dysfunctions affect the organization of behavior, i.e. how schizophrenic patients put individual behavioral elements together to form characteristic patterns. To this end, we use a simple experimental task to elicit sequences of behavior and apply nonlinear dynamical techniques to extract the underlying order in these sequences. It has been proposed that the temporal organization of behavior in schizophrenia patients may be closely linked to the functional status of the dopamine system, which is thought to facilitate the competition between different behavioral options (Lyon and Robbins, 1975; Lyon et al., 1994).

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Previous studies have shown that the behavior of individual schizophrenic patients in the choice task paradigm is not random (Frith and Done, 1983; Paulus et al., 1994) but shows large fluctuations between highly predictable and highly unpredictable subsequences when compared to normal control subjects (Paulus et al., 1996). In addition, 'long-range correlations' between choices have been found for control subjects, reflecting a surprisingly long-lasting effect of each individual choice on subsequent behavior that creates a unique cognitive 'signature' of the individual subject (Paulus, 1997).

Experimental findings suggest that in complex systems ranging from DNA coding sequences (Peng et al., 1992a) to symptoms in bipolar (Gottschalk et al., 1995) or schizophrenic disorders (Duenki and Ambuehl, 1996) as well as stereotyped movements (Kropla et al., 1994), fluctuations of critical variables occur across many scales. Scaling in natural systems refers to the observation that similar rules apply across many different spatial and temporal domains because subsystems interact significantly with one another. The inability to separate non-interacting subsystems supports the idea that individual experimental observations in complex systems cannot be viewed in isolation (Stanley et al., 1996). If this interaction applies to human behavior in general and behavior of schizophrenic patients in particular, then each behavioral element would contribute to an emerging behavioral pattern. Moreover, these 'scaling relationships' have important implications for the manipulation and modeling of complex systems and suggest that small changes on one scale of observation may propagate to affect the macroscopic configuration of the system. For example, it has been argued that scaling behavior in the human heart reflects complex regulatory mechanisms that maintain adaptability to changing environmental stimuli (Peng et al., 1992b). The current report tested the hypothesis that these observations can be extended to include scaling relationships in sequences of human behavior in general, and dysregulations of behavioral sequences in schizophrenic patients in particular. The central focus of this investigation was to determine whether the behavior of schizophrenic patients is more appropriately described by a system with limited, short-range interactions or is due to a complex system with long-range, non-random relationships between its behavioral elements. In addition, we aimed to quantify the degree to which the behavior is 'driven' by the random presentation of an external stimulus.

Schizophrenic patients exhibit difficulty in tests of learning, problem-solving and planning (Goldberg et al., 1990; Braff et al., 1991; Pantelis et al., 1997), and these types of deficits have been interpreted as reflecting a dysregulated fronto-striatal system (Robbins, 1990). Theoretically, these deficits may result from two underlying hypothetical dysfunctions: First, the behavior of schizophrenic patients may be abnormally dependent on previous behavior and thereby not adaptive to the current environment. Second, the information processing resources of these patients may be allocated abnormally to internal processes rather than to the processing of environmental stimuli.

This abnormal inner directedness has long been recognized as a primary feature of schizophrenia and was described as 'autism' by Bleuler (1950). As a result of an autistic predisposition, external stimuli may fail to appropriately influence the process of response formation. To test these hypotheses, the mutual information function of sequences of responses generated in a choice task paradigm was calculated to determine the level of association within behavioral sequences and to address two fundamental questions. First, is the current behavior of schizophrenic patients relative to comparison subjects differentially more influenced by previous behavior? Second, are schizophrenic patients relative to comparison subjects differentially less influenced by external stimuli?

2. Methods

2.1. Subjects

Twenty-four control subjects (12 males and 12 females), ranging from 18 to 50 years of age (mean 26.6 ± 1.97), and 31 schizophrenic patients (21 males and 10 females) ranging from 20 to 52 years of age completed the choice task paradigm as part of a larger study [for details, see Cadenhead et al. (1997)]. The average age of onset and duration of illness for the schizophrenic patients was 21.24 ± 1.19 and 15.19 ± 1.43 years, respectively. The patients were treated with a variety of antipsychotic medications corresponding to an average Chlorpromazine equivalent (Kessler and Waletzky, 1981) of 764.9 ± 135.4 mg daily.

2.2. Testing

The two-choice guessing task comprises a simple 'game-like' situation in order to maximize the subject's participation and motivation. The subject is asked to sit in front of a computer, and a short description of the task is provided on the computer screen. Specifically, the subject is told that there is a house in the center with people inside. Two people are shown, one to the left and one to the right of the house. The task is to 'help' the people on the screen to get a ride with a car, which comes by on the left or the right side. In order to get to the car, the person must cross a ditch. The subject can build a bridge on either the left or right side by pushing the left or right mouse button. The subject is not told where the car will come by, and is asked to push the left or right button where the subject thinks that the car will come by. Following the response, the car is shown briefly (250 ms), and a new trial begins immediately. The choice task paradigm consists of 500 trials, and each trial is randomly reinforced with probability $p=0.5$ using a random number generator. The subject's and the computer's choices as well as the inter-trial-interval are stored on the computer for subsequent analyses.

2.3. Analysis

The mutual information function (Shannon and Weaver, 1949) quantifies the linear and non-linear spatial and temporal relationship between events in units of information (bits). Given a distribution, P, and the individual probability density of finding state j, p_j, the entropy of this distribution is given by $H_P = -\sum_j p_j \log p_j$. Given two distributions, P and Q, the entropy of the joint probability, PQ, is given by $H_{PQ} = -\sum_{i,j} p_{i,j} \log p_{i,j}$, and their mutual information is given by the expression $I = H_p + H_Q - H_{PQ}$. This number characterizes the amount of information that is shared between the two distributions. More recently, this function has been applied to non-linear time series similar to the quantitative description of linear systems using the autocorrelation function. Specifically, given two events within the same time series that are separated by k intermediate events, the mutual information can be computed by evaluating the joint probability of the first to the $N-k$th event with the kth to the Nth event. It can be shown that the joint probability distribution of a series of random events is given by the product of the probability distribution of the individual events and that any non-random relationship between events results in a systematic decrease of the joint probability entropy (Khinchin, 1957). The variable k is known as the delay of the mutual information and corresponds to a particular temporal scale. Many physical systems with limited, short-range interactions are characterized by a decay of the mutual information of the form $I_k = A \exp(B \times k)$, known as exponential decay, indicating that two events are unrelated after a finite number of steps. In contrast, complex physical systems show a decay characteristic that is more appropriately described by $I_k = A\, k^{-B}$, known as logarithmic decay, leading to significant non-random relationships for large values of k. The cross-mutual information was calculated based on the entropy of the presentation of the first $N-k$ presentations of the car, $H_{c,\, 0 \ldots N-k}$ and the kth to the Nth choice, $H_{k \ldots N}$ via $I_k = H_{c,\, 0 \ldots N-k} + H_{k \ldots N} - H_{c, 0 \ldots N-k, k \ldots N}$. In order to examine the effect of the finite length of the time series (500 trials), calculated the mutual and cross-mutual information function of a time series with the same number choices but no sequential order. Specifically, a surrogate data series was generated for each subject by randomizing the choice sequence using a simple shuffling algorithm.

For the statistical analyses, two measures were obtained to compare schizophrenic patients with controls. For each subject, the maximal correlation length was determined by obtaining the maximal delay of the mutual information whose confidence interval did not include zero. Morever, the influence of the previous stimulus on the current choice was determined by obtaining the lag 1 cross-mutual information. In addition, the logarithmic decay rate and the intercept of the mutual information function was computed for each subject. These variables were subjected to a multivariate Hotelling's T^2 analysis and an analysis of covariance (ANCOVA) using the BMDP software package (Dixon, 1988).

3. Results

Fig. 1 shows a double-logarithmic plot of the average mutual information for control subjects, schizophrenic patients, and for the shuffled data sets of both groups. In addition, the decay functions for $k=1$–10 for the comparison subjects and for $k=1$–128 for the schizophrenic patients were fitted with linear least-squares fits and correspond to the straight lines. This analysis suggests that the decay of the mutual information function for both control subjects and schizophrenic patients is of the form $I_k = A\,k^{-B}$, i.e. a power-law decay that is characteristic of complex physical and biological systems. Alternative models using an exponential or linear decay of information yielded significantly poorer fits with increased and trended residuals. The group decay coefficient ($\pm$SEM) for comparison subjects ($B_c = 1.498 \pm 0.098$, $r^2 = 0.96$) was significantly larger than that for schizophrenic patients ($B_s = 0.712 \pm 0.027$, $r^2 = 0.83$). Thus, for schizophrenic patients, the previous choices exert a significantly larger and longer-lasting influence over subsequent choices. The maximal delay of the mutual information that was significantly greater than zero was significantly larger [$F(1,52) = 4.23$, $p < 0.05$] for schizophrenia patients (ANCOVA adjusted mean 35.06 ± 7.44) than for controls (ANCOVA adjusted mean 10.71 ± 8.56) and was not significantly affected by the influence of the previous stimulus [$F(1,52) = 1.43$, n.s.].

Fig. 2 displays the cross-mutual information function quantifying the association between the information contained in the presentation of the stimulus and the subsequent kth choice. Specifically, this figure shows the average cross-mutual information function ($\pm$SEM) for 25 normal control subjects and 31 schizophrenic patients. This function quantifies for the first time the extent to which schizophrenic patients utilize less external information to generate their responses. The maximal influence exerted by the information contained in the location of the car is found for the first choice following the presentation of the car, i.e. the previous location of the car has the most influence on the subsequent left or right choice alternative. The influence of the car on the choice selection decays quickly and reaches levels

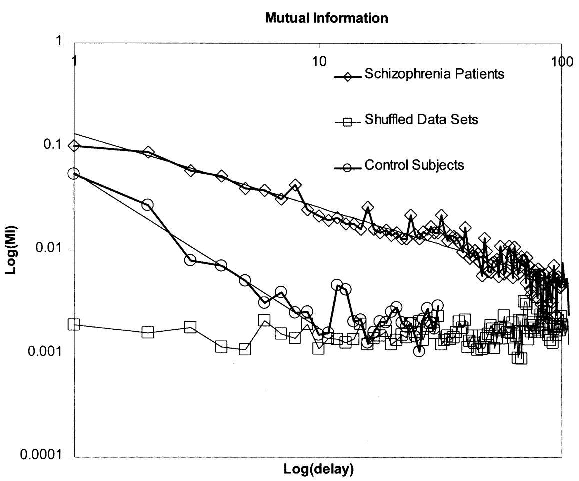

Fig. 1. Mutual information.

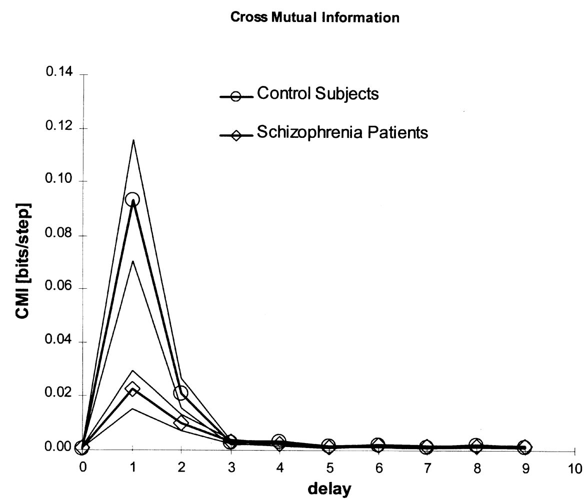

Fig. 2. Cross-mutual information.

indistinguishable from noise at a delay of three steps, indicating that the stimulus influences only a limited number of subsequent choices. While the location of the car contributes approximately 9.3% (0.093 bits ± 0.02) to the subsequent choice for control subjects, the same information contributes only 2.3% (0.023 bits ± 0.007) to the choice in schizophrenic patients [$F(1,52) = 6.90$, $p < 0.05$]. In other words, the behavior observed in the choice task in controls is about fourfold more susceptible to the influence of the external stimulus provided on the computer screen when compared to schizophrenic patients. In contrast, the immediate past choice contributes approximately 11% (0.10 bits ± 0.02) to the current choice for schizophrenic patients compared to 5% (0.053 bits ± 0.01) for controls.

4. Discussion

This investigation yielded two main differences between normal controls and schizophrenic patients. First, the current response of schizophrenic patients on the choice task depends on a long set of previous responses and is significantly more influenced by previous responses when compared to controls. Second, in examining the interaction of stimulus location and responses, the current response of schizophrenic patients is substantially less influenced by the immediate previous location of the external stimulus relative to controls. In combination, these results suggest that the system underlying the generation of the behavioral sequences in this task is not characterized by limited, short-range interactions but is a complex system with long-range and significant non-random relationships between its behavioral elements. Moreover, these results support the hypotheses that the behavior of schizophrenic patients relative to comparison subjects is abnormally dependent on previous behavior and is characterized by the allocation of fewer processing resources to external stimuli.

Alternatively, these results might be interpreted to reflect an overall lack of attention to or engagement in the task. However, there are several quantitative and qualitative indicators that lead to a rejection of this interpretation. First, the increased long-range correlation between choices in schizophrenic patients is independent of the decrease in influence of the immediate preceding stimulus as indicated by the ANCOVA results. Second, observations during this task revealed that patients were engaging in the task, commenting on different outcomes, and making statements about the underlying rule of the presentation of the car. Third, the logarithmic dependence of the current choice on the previous responses does not reflect a lack of engagement, attention or perseveration of responding which has been reported in a variety of paradigms (Siegel et al., 1976; Sullivan et al., 1993; Goldberg et al., 1994; Elliott et al., 1995). Specifically, a combination of uncorrelated runs due to random responding reflecting disengagement in the task or simple perseverative responding would result in an exponential decay of correlations. However, the logarithmic dependence points toward a organized association of choice sequences across a large range of responses. Thus, the complex organization is not unlike that observed in the fluctuation of clinical symptomatology (Duenki and Ambuehl, 1996) and in temporal organization of sequential responding as shown previously by Lyon et al. (1994).

The mechanism underlying long-range correlations has been studied in mathematical non-linear dynamical systems (Manneville, 1980) and in complex physical or biological systems consisting of many interacting elements (Stanley et al., 1992). There are two possible, albeit not competing, explanations. The phenomenon of intermittency has been investigated as the principal source of long-range correlations in non-linear dynamical systems (Manneville, 1980). Intermittency is defined as a temporal sequence of observations, which are organized in the vicinity of a nearly stable fixed-point, i.e. an observational point that does not change over time. However, this seemingly coherent temporal behavior is interrupted by highly unpredictable events. Intermittency has been proposed as a critical factor in the transition from health to illness and illness to health (Mandell, 1983). Alternatively, correlated random walk models based on probability distributions with large variability have been used to explain long-range correlations in many natural systems (Shlesinger and West, 1988). Based on these findings, long-range correlations in the choice task could be due to a reduced number of strategies that are used for a large number of choices. Specifically, if response strategies can extend over a few choices, i.e. changing the strategy after two or three responses, or over many choices, i.e. in the order of 500 in this task, then the correlation between choices decays logarithmically. This logarithmic decay indicates that small-scale changes propagate to large-scale changes giving rise to a scaling phenomenon. Similar scaling properties have also been observed in inter-response intervals of stereotyped motor movements (Kropla et al., 1994).

The existence of long-range correlations has other implications for research addressing the information processing characteristics of schizophrenic patients. First, schizophrenic patients have difficulty incorporating rule-learning and continue to perform poorly and perseveratively on the Wisconsin Card Sorting Task despite being told about the underlying rules (Goldberg and Weinberger, 1988). These perseverative tendencies may reflect the process involved in the reduced influence of external stimuli on the patients' behavior reported here. Second, many psychological and neuropsychological paradigms involve detailed analyses of stimulus–response relationships in terms of appropriate versus inappropriate responding or in terms of differential response times. Underlying the analyses of these behaviors is the assumption that behavioral responses are relatively specific to the current situation and are not influenced significantly by previous behaviors. The present results illustrate that the individual behavioral responses of a schizophrenic patient cannot be considered in isolation. Instead, each current response must be understood in terms of previous behavior extending over a large temporal scale. Third, these results may ultimately shed light on the dynamical status of the neural circuitry involving prefrontal cortex and the cortico-striato-pallido-thalamic (CSPT) neural circuitry (Swerdlow et al., 1992). The state of the CSPT circuit is thought to adaptively modulate response initiation and sequencing in response to external and internal stimuli. Fourth, other investigators have proposed that the rapid response switching results in long stereotypic runs reflecting the increase in 'internal driving' of the dopaminergic system (Lyon et al., 1994). The current investigation is an independent confirmation of this complex temporal behavior. Moreover, this finding is extended to show that similar organizational principals operate across many different biological and physical systems including human behavior. Future research will need to identify the neural substrate underlying the organization of choices in this paradigm and its dynamical characteristics to elucidate further the brain–behavior relationships in schizophrenic patients. The current data suggest that a critical deficit in schizophrenia may be a maladaptive dynamical state in which the patient cannot respond to changes in the stimulus environment but rather responds to 'autistic' rules based on non-interruptible, self-generated schemata.

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