
Trait Contributions of Complex Dysregulated Behavioral Organization in Schizophrenic Patients

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Background: *The “temporal architecture” of behavior is a construct that can be used to quantify the structure of behavioral sequences in the temporal domain—for example, by using a two-choice prediction task to investigate how past responses, stimuli, and outcomes influence the decision-making process. Using this task, previous investigations of the temporal architecture of the behavior in schizophrenic patients have identified an increased frequency of alternating highly predictable and highly unpredictable response sequences in the same test session in the same patient. Here, the hypothesis is tested that this dysregulation is stable over time and independent of psychosocial factors and symptomatic fluctuations.*

Methods: *Ninety-one schizophrenic patients were tested on a 128 trial version of the two-choice prediction task; of those, 58 subjects completed a retest session 40 days later. Three sets of measures were obtained: simple response biases, dynamical entropy, and mutual information functions. These measures were subjected to a factor analysis, and the reliability of the resulting factors was examined.*

Results: *First, three factors were obtained, which quantify 1) the level of dysregulation on this task; 2) the extent to which a win-stay/lose-shift strategy was used; and 3) the amount of simple response perseveration. Second, Cronbach α for these factors was .699, .721, and .458, respectively. Third, there were no significant differences in the level of these factors within individual patients at the two time points. Fourth, neither symptom measures (Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms subscale scores) nor psychosocial or clinical variables (age, gender, illness duration, medication status) were able to predict the level of these factors at test or at retest.*

Conclusions: *These results support the hypothesis that the fundamental dysregulation of the temporal architecture of behavior in schizophrenic patients is stable across time and independent of symptomatic status. Future studies will examine the heritability of this dysfunction.* Biol Psychi-

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Key Words: Schizophrenia, decision making, dysregulation, trait, intermittency, behavior

Introduction

Schizophrenia is a complex disorder that comprises a wide range of clinical symptoms and shows a high variability in clinical course (van der Velde 1976). Several investigators have proposed to redefine the clinical phenotype of schizophrenia in terms of a fundamental underlying cognitive dysfunction (Green and Nuechterlein 1999; Weinberger 1999). Andreasen (1999) and Andreasen et al (1999) have argued that schizophrenia is a single illness with a single phenotype that is defined by a fundamental cognitive abnormality. These authors have proposed that schizophrenic patients suffer from cognitive dysmetria, which is characterized by a disruption of the fluid, coordinated sequences of thought and action. In contrast, Braff (1999) has suggested that the fundamental deficit, if it exists, has not yet been identified via the methods of traditional neuropsychological or neurocircuit models.

Several mechanistic models have been proposed to account for some or all of phenomenology observed in schizophrenic patients. These models are based on the distributed neural circuitry that has been implicated in the neuropathology of schizophrenia and emphasize changes in the connection between neural substrates in the spatial and temporal domain. Cohen and Servan-Schreiber (1992), using a parallel distributed processing model, suggested that the inability to use contextual information in schizophrenic patients is due to a lack of proper prefrontal activation to hold information online. McCarley et al (1999) have pointed out that schizophrenic patients exhibit an over- or under-activation of neural networks, presumably due to lack of autoinhibition. Friston (1998) has argued that the cognitive deficits in schizophrenic patients are due to a disconnectivity syndrome between frontal and temporal neuronal populations. Experimen-

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tally, these formulations are consistent with recent studies of the spread of activation in semantic space using a semantic decision-making task (Aloia et al 1998; Goldberg et al 1998). Computationally, neural network models of schizophrenia have provided evidence for the temporal domain dysfunction (Hoffman 1987; Hoffman and McGlashan 1997).

In previous investigations, we have developed a theoretical and experimental framework to assess the association of behavioral acts across time (Paulus et al 1994, 1996, 1999a). The sequential characteristics of responses can be comprehensively quantified by techniques that have been used to measure the degree of randomness in mathematical (Ruelle 1978) and physical systems (Herzel and Grosse 1995). This sequential approach enables one to examine the hypothesis that the fundamental cognitive dysfunction in schizophrenia is in the temporal domain, i.e., the association of thoughts and actions is dysregulated over time. A simple decision-making test, the two-choice prediction task (Frith and Done 1983; Lyon et al 1986) can be used to obtain sequences of behavior in the presence of uncertain but controlled stimulus conditions. The initial findings of responses sequence characteristics in schizophrenic patients during the two-choice prediction task support the general hypothesis of a cognitive dysfunction in the temporal domain. Specifically, schizophrenic patients generate more response sequences that are rigid and highly predictable as well as more response sequences that are chaotic and highly unpredictable in the same test session in the same patient (Paulus et al 1996). Moreover, the response on this task depends on a long history of previous responses yielding long-range correlations across sequences of responses (Paulus et al 1999a).

In nonlinear dynamics, systems that exhibit large fluctuations of state with distinct dynamical characteristics are often found to exhibit a phenomenon called intermittency (Manneville 1980). In these systems, seemingly coherent and predictable sequences of observations are interspersed with highly unpredictable sequence of observations for a short period of time (Heagy et al 1994). These systems are ubiquitous in nature (Mandell 1983; Peng et al 1993; Stanley et al 1995) and are characterized by long-range correlations (Sato and Honda 1990) due to the long segments of coherent sequences. In this context, long-range correlations correspond to the observation that schizophrenic patients generate long sequences of responses (i.e., 40-60 consecutive choices) during the two-choice prediction task that are highly predictable. Similarly, other investigators (Duenki and Ambuehl 1996) analyzing temporal patterns of symptoms in schizophrenic patients have proposed that intermittency may play an important role in this illness.

If behavioral intermittency reflects an underlying phys-

iological process caused by the fundamental dysregulation of the temporal architecture of behavior, then this cognitive dysfunction should characterize patients across time and might well be independent of clinical symptomatology or socio-demographic characteristics. Thus, the central aim of this investigation was to determine whether the dysregulated temporal architecture of behavior in schizophrenic patients is stable across time and whether behavior on this task is related to socio-demographic characteristics and clinical symptoms. Two specific hypotheses were examined. First, the behavioral factors that characterize performance on the two-choice prediction task are stable and reliable across test sessions. Second, neither socio-demographic characteristics nor clinical symptoms predict performance on the two-choice task.

Methods and Materials

Subjects

Ninety-one (66 male and 25 female; 50 Caucasian, 14 Hispanic, 11 African American, 2 Asian, and 14 mixed or other racial group) subjects with a DSM-IV (American Psychiatric Association 1994) diagnosis of schizophrenia were tested in this study. Patients were diagnosed using the structured clinical interview for DSM-IV diagnoses (SCID-IV; First et al 1995). The subject's average age was 39.9 ± 0.9 years (range 26-62), and they had an average of 12.3 ± 0.25 years of education (range 8-20). The average duration of illness was 17.3 ± 1.3 years (range 0.3-43.5). Medication status was available for 63 of the 91 subjects: 23 subjects were treated with typical antipsychotic medications, 26 subjects were treated with atypical antipsychotic medications (including clozapine, risperidone, olanzapine, and quetiapine) and 11 patients were treated with both. Three subjects were not on medications. Informed consent was obtained from each patient before testing (University of California San Diego Human Subjects Committee #980772). Each subject received a comprehensive psychiatric assessment and medical evaluation including toxicological screening. The Scale for the Assessment for Positive Symptoms (SAPS; Andreasen 1984b) and Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984a) symptoms were used to evaluate symptom levels. Complete symptom assessments were available from 46 patients at both test and retest. Following the psychiatric assessment, each subject completed the two-choice prediction task (described below). Of the 91 subjects, 58 subjects completed the two-choice prediction task again 40.1 days \pm 2.2 (range 7-79) later. These data were used to calculate the reliability and stability of the behavioral measured obtained from the task.

Two-Choice Prediction Task

Each subject was given instructions on the computer screen. Briefly, a house is shown in the center of the computer screen with a person on the left and right side. The subject is told that a car will appear on the left or right side. The task for the subject is to predict where the car will appear. The subject is told that the

car will appear briefly (300 msec) *after* a response has been made. The subject uses a left or right mouse button to decide where he/she thinks the car will come by. A new trial begins immediately after the display of the car. The subject is not given any information about the sequence of stimulus presentations. The two-choice prediction task consists of 128 trials; the presentation of the car is based on the subject's response. Specifically, the subject "correctly" predicts the location of the car in 64 trials. The sequence of "correct" predictions is random. The basic measures consist of the subject's response, the presentation of the car, and the latency to select a response, i.e., the time from the beginning of the trial to the button press.

Measurements

Three sets of measures were obtained from the sequences of responses to assess 1) whether subjects exhibit response biases; 2) whether the current response can be predicted by the previous response, the previous presentation of the stimulus, or the previous outcome of the prediction; and 3) whether the current response was part of a highly predictable or highly unpredictable response sequence. First, response bias measures were obtained to determine whether subjects were more likely to select RIGHT versus LEFT or were more likely to SWITCH between responses than to STAY with the same response. Second, the mutual information function was used to determine the degree of nonrandomness between two observations. Mutual information functions (Herzel and Grosse 1997) are based on the logarithmic likelihood ratio between the observed frequency of an event and the expected frequency of an event. These functions quantify the degree to which the co-occurrence of two observations is above chance level in units of bits. For example, if the subject selects the LEFT response more often when the car was shown previously on the left side, the mutual information will quantify the bits of information contained in the response selection due to knowing the previous location of the car. Specifically, the sequence of responses and the sequence of stimulus presentations were coded in such a way to examine the relationship between the current response and the previous response (LEFT or RIGHT), the current response and the previous stimulus (car on the RIGHT or LEFT), and the current response and the previous outcome ("correct" prediction or "incorrect" prediction). Third, the dynamical entropy was computed for sequences of responses to quantify the degree of response sequence uncertainty. These behavioral analyses were based on techniques that have been developed in the context of nonlinear dynamical systems (Eckmann and Ruelle 1985), complex physical systems (Haken 1996), and statistical mechanics of physical (Fujisaka and Inoue 1990) and dynamical systems (Ruelle 1978). The degree of dysregulation was defined by the range of subsequence entropies, i.e., $h_{\text{diff}} = h_{\text{max}} - h_{\text{min}}$. A small number signifies that most response subsequences are similarly predictable. In contrast, a large number indicates that some response subsequences are highly predictable and other response subsequences are highly unpredictable during the same test session.

First, to use a minimal set of variables that quantify the behavioral factors that characterize performance on the two-choice prediction task by schizophrenic patients and to determine

Table 1. Symptomatic Assessment of Schizophrenic Patients for Both Test and Re-test Based on Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS).

SANS and SAPS subscales	Test		Retest		Paired <i>t</i> test	Significance
	Mean	SD	Mean	SD		
Affective blunting	1.76	1.4	1.85	1.2	-0.56	ns
Alogia	1.5	1.35	1.47	1.36	0.18	ns
Avolition	1.87	1.47	1.98	1.29	-0.52	ns
Anhedonia	2.24	1.4	2.28	1.28	-0.14	ns
Attention	1.26	1.36	1.15	1.35	1.12	ns
Hallucinations	2.24	1.37	1.87	1.64	2.40	.02
Delusions	2.7	1.17	2.6	1.47	0.65	ns
Bizarre behavior	1.52	1.17	1.72	1.28	-1.03	ns
Formal thought disorder	1.67	1.35	1.34	1.46	2.36	.02

n = 46.

whether the previously reported behavioral factors obtained from this task could be replicated, a factor analysis was conducted. The following variables were entered into the analysis: probability of choosing the RIGHT response; SWITCH response; the degree to which the previous choice predicted the current choice (MI); the degree to which the location of the previous stimulus predicted the current choice (CMI); the degree to which the previous situation predicted the current choice (SMI); the degree to which a win-stay/lose-shift strategy predicted the current choice (WSMI); the average response sequence uncertainty (HMET); and the degree of dysregulation (HDIFF) (means and standard deviations are shown in Table 1). Using an eigenvalue > 1.0 criterion and a varimax rotation, factor scores were computed for each patient. Second, the factor regression coefficients were used to calculate these scores from the choice task measures for the retest condition. Third, to assess reliability of the response characteristics on this task, a two-factor (subjects, measurement) random effect model analysis of variance (ANOVA) was used to obtain intraclass correlation coefficients and Cronbach α for each factor. Fourth, stepwise multiple linear regression and planned nonparametric Spearman rank correlations were used to determine the relationship between socio-demographic variables (age, education), symptoms (SAPS, SANS), or illness duration and the factors describing the behavioral variation on the two-choice prediction task. Fifth, to determine whether medication significantly affected performance on the task, patients were separated into three groups (treatment with typical antipsychotics, atypical antipsychotics, or both). Sixth, independent *t* tests were conducted to determine the effect of gender on decision-making behavior.

Results

Factor Analysis

The factor analysis extracted three independent factors explaining 83.4% of variance of the response bias measures, the mutual information functions, and the entropy measures. The correlations between the two-choice pre-

Table 2. Average Behavioral Measures for 91 Schizophrenic Patients who Were Entered into the Factor Analysis

Descriptive statistics	Mean	SD	<i>t</i> score
Probability choosing left	0.517	0.087	1.879
Probability of switching	0.527	0.173	4.815
$H_{\max} - H_{\min}$	1.086	0.452	2.622
Metric entropy	0.732	0.153	-6.408
Mutual information	0.091	0.169	8.692
Cross mutual information	0.124	0.149	-1.117
Situational mutual information	0.229	0.191	0.828
Win-Stay mutual information	0.128	0.148	-1.053

t score differences are shown based on a 78-subject control group.

diction task measures and the extracted factors following a varimax rotation are shown in Table 2. The correlation pattern between the measures and the first factor supports the results of a similar analysis with a different cohort of patients that also extracted a "dysregulation factor." A high loading on the first factor indicates that subjects fluctuate between highly predictable and highly unpredictable choice sequences and show a decreased average predictability. In addition, high scores indicate that the current choice can be predicted by the previous choice irrespective of the external stimulus or outcome. The correlations between the measures and the second factor also support the previously reported "win-stay/lose-shift" factor. Specifically, a high loading on the second factor characterizes subjects whose current choice can be predicted by the previous location of the car (i.e., *left* or *right*) and the previous outcome (i.e., *correct* or *incorrect*). In particular, a high loading indicates that subjects choose the same response if the previous choice was correct (win-stay) or switch to the alternate response if the previous choice was incorrect (lose-shift). The correlations between the measures and the third factor support the notion of a "response perseveration" factor. Specifically, a high loading on this factor indicates that subjects have a higher propensity to select the left response and to switch between responses irrespective of the previous outcome.

Factor Reliability

The factor score coefficient matrix from the factor analysis of the 91 schizophrenic patients was used to compute factor scores for the 58 schizophrenic patients that completed the two-choice prediction task an average 40 days later. A mixed ANOVA showed that the "dysregulation" factor score did not differ between test and retest [$F(1,57) = 0.63$, ns]. The average intraclass correlation coefficient or Cronbach α using a two-way mixed effects model was .699 (95% confidence interval, .492-.822) and highly significant [$F(1,57) = 3.30$, $p < .01$]. A similar analysis for the "win-stay/lose-shift" factor revealed no

significant differences between tests [$F(1,57) = 0.63$, ns] and an average intraclass correlation coefficient of 0.721 [95% confidence interval, 0.529-0.835; $F(1,57) = 3.65$, $p < .01$]. Finally, the "response perseveration" factor did not differ between tests [$F(1,57) = 1.12$, ns] and was characterized by an average intraclass correlation coefficient of 0.458 [95% confidence interval, 0.08-0.68; $F(1,57) = 1.84$, $p < .05$].

Two-Choice Prediction Task and Socio-Demographic Variables

There was no significant difference of the factor scores [dysregulation, $t(90) = 1.54$, ns; win-stay/lose-shift, $t(90) = 0.24$, ns; response perseveration, $t(90) = 1.26$, ns] between male and female subjects. Spearman rank correlations did not reveal a significant correlation between age, education, or illness duration and the dysregulation or the win-stay/lose-shift factor. Illness duration but not age correlated with the response perseveration factor. Specifically, subjects with longer illness duration showed a higher degree of response perseveration (Spearman $\rho = .30$, $p < .01$).

Two-Choice Prediction Task and SANS and SAPS Subscales

The SANS and SAPS subscale scores (Table 3) were entered into a step-wise regression to determine whether symptom status was able to predict performance on the two-choice prediction task. None of the symptom variables entered into a regression model to predict the dysregulation factor, the win-stay/lose-shift factor, or response perseveration factor.

Two-Choice Prediction Task and Medication Status

A one-way ANOVA did not show a significant effect of medication status on the dysregulation factor [$F(2,57) = 0.827$, ns], the win-stay/lose-shift factor [$F(2,57) = 0.797$, ns], or the response perseveration factor [$F(2,57) = 1.297$, ns].

Discussion

This investigation yielded three main results that provide support for the two hypotheses. First, all three behavioral factors underlying the performance on the two-choice prediction task that were obtained in a previous cohort of schizophrenic patients (Paulus et al 1999b), i.e., dysregulation, win-stay/lose-shift, and response perseveration, were replicated in this study. Second, two of these factors (dysregulation and win-stay/lose-shift behavior) exhibit reliability coefficients of 0.7, which supports the first

Table 3. Correlation Patterns of the Rotated Factor Solution with the Original Variables

Variables	Factor 1: dysregulation	Factor 2: win stay/loshesift	Factor 3: response preservation
Probability choosing right	.232	-.110	-.831
Probability of switching	.298	-.169	.699
$h_{\max} - h_{\min}$.749	-.116	-.122
Metric entropy	-.927	.173	.057
Mutual information	.908	-.077	.266
Cross mutual information	-.217	.965	-.071
Situational mutual information	.655	.711	.173
Win-Stay mutual information	-.192	.970	-.045
% variance explained	36	31	16

Correlations with $r > .50$ are in boldface.

hypothesis that the behavioral factors characterizing performance on the two-choice prediction task are stable and reliable across test sessions. Third, neither symptoms nor socio-demographic variables were able to predict performance as measured by the factor scores on the two-choice prediction task. Thus, the temporal architecture of responding on this task is both “abnormal” and seems “fundamental,” i.e., independent of state-related factors.

As a corollary, medication status, although not rigorously controlled, had no significant effect on dysregulation, win-stay/lose-shift behavior, or response perseveration; however, it is important to note that the current finding does not imply that dysregulation of decision-making during this task cannot be changed by controlled therapeutic interventions. Future investigations will examine whether atypical antipsychotic medications are able to reverse or ameliorate this expression of the observed patterns of rigid or highly unpredictable behavior.

Decision making reflects the process of transition from thoughts to actions. The two-choice prediction task (Frith and Done 1983; Lyon et al 1994, 1986) enables one to examine this highly dynamic process and can be used to determine how this process changes over time. The mutual information functions and entropy analyses can be used to extract organizing principles underlying the decision-making process to link observed behavioral to underlying thought strategies (Paulus 1997; Paulus et al 1994, 1996). These analyses revealed that the decision-making dysfunction in schizophrenic patients is not uniformly disturbed. Specifically, patients do not generate either overly rigid or overly unpredictable response sequences throughout the test session. Instead, schizophrenic patients show both rigid and chaotic response sequences during the same test session. This study shows that the degree to which patients fluctuate between rigid and unpredictable response sequences, i.e., the dysregulation factor underlying the two-choice task performance, is stable across two test sessions that are separated by more than 30 days. Moreover, the inability to predict the performance on the choice

task from symptom measures supports the hypothesis that the disturbance of the temporal architecture as measured by this task is relatively independent of the positive and negative symptomatic status of the patient at time of testing. This finding is similar to that of Green et al (2000) that neurocognitive deficits in schizophrenic patients do not relate to psychotic symptoms but do relate to fundamental outcome.

This fundamental disruption of the temporal architecture of behavior, i.e., the temporal nonuniformity of the dynamical characteristics of the response sequences during the two-choice prediction task, is consistent with mechanistic (Cohen and Servan-Schreiber 1992; Friston 1998), neural network (McCarley et al 1999), and computational models (Hoffman 1987) that emphasize the disrupted connectivity between individual neuronal, behavioral, or cognitive elements. Mechanistically, one may speculate that the sequential strategies underlying the selection, ordering, and sequencing of the responses during the two-choice prediction task at any given point in time are subject to competing processes. These processes may reflect different rule sets that relate past behavior and past stimuli to current behavior. The degree of dysregulation factor quantifies the extent of switching between different strategies during this task, the win-stay/lose-shift factor quantifies the degree to which the current choice is dependent on the previous outcome, and the response perseveration factor measures the extent to which subjects engage in repetitive, outcome-independent response selection. As pointed out by other investigators (Elliott and Dolan 1998; Elliott et al 1999), hypothesis-testing and outcome evaluation are critical components of this task. An intermittent disruption of these processes may lead to a temporary reduction of strategy switching or outcome-dependent response selection. This disruption can result in highly predictable response sequences. In contrast, intermittent increase in strategy switching or outcome-dependent response selection can lead to an increase in highly unpredictable response sequences, due to the fact that the

presentation of the car is random. Therefore, a disrupted competition between these rule sets can lead to an “oscillating dysregulation” between highly predictable and highly unpredictable subsequences within a single test session. Finally, the hypothesis of a disruption of the temporal architecture of behavior characterized by an oscillating dysregulation is supported by a recent finding that schizophrenic patients relative to control subjects show increased fluctuations in P50 gating (Patterson et al 2000). Future studies will examine whether schizophrenic patients exhibit this oscillating dysregulation in other information processing, cognitive, or behavioral paradigms.

This study has several limitations. First, neuropsychological assessment was not obtained for this group of subjects. Therefore, the interpretation of the factors is limited to the correlation of the factors with the basic response bias measures, the mutual information, and dynamical entropy measures. Future studies will examine more carefully the relationship among dysregulation, win-stay/lose-shift behavior, response perseveration, and standard measures of executive functioning, attention, and memory. A previous study supports the hypothesis that measures of executive functioning, i.e., performance on the Wisconsin Card Sorting Task, predict the degree of dysregulation and therefore further links the dysregulation of prefrontal functioning (Paulus et al 1999b). Second, there was no direct measure of interest in performing the task. One approach to examine the subject’s attention to or interest in the two-choice prediction task is to vary reinforcement conditions and to monitor whether the response characteristics change accordingly. Therefore, future studies will include different task conditions to measure the degree to which the subject is attending to the task. Third, a critical step to determine whether the factors quantifying performance on this task can be used to assess the fundamental cognitive dysfunction in schizophrenic patients is to determine the degree to which dysregulation, win-stay/lose-shift behavior, or response perseveration are heritable. Future studies will examine this by obtaining family data on the two-choice prediction task. Fourth, this study does not address the specificity of the dysregulation, win-stay/lose-shift behavior, or response perseveration for schizophrenia. Comparing the response characteristics of schizophrenic patients with affective disorder and anxiety disorder patients will be necessary to determine whether the response characteristics are unique to schizophrenic patients or reflect a general response bias of subjects with mental disorders.

In conclusion, this study provides further evidence that the temporal architecture of behavior in schizophrenic patients is dysregulated and that this dysregulation consists of an oscillation between rigid or highly predictable

response sequences and chaotic or highly unpredictable response sequences. Moreover, the degree to which schizophrenic patients exhibit dysregulation on this task is stable across sessions and may be used as an intermediate phenotype to further quantify the fundamental cognitive dysfunction in patients with schizophrenia. Examining the temporal architecture of behavior using nonlinear measures of response sequences allows one to investigate the temporal dimension of the brain–behavior relationships and enables one to pose new hypotheses about the fundamental brain dysfunction underlying schizophrenia.

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