Decision-Making Dysregulation in First-Episode Schizophrenia

Katja Cattapan-Ludewig, MD,† Stephan Ludewig, PhD,† Nadine Messerli, PhD,* Franz X. Vollenweider, MD,‡ Antonia Seitz, MSc,†§ Joram Feldon, PhD,§ and Martin P. Paulus, MD‖*

Abstract: Studies with chronic schizophrenia patients have demonstrated that patients fluctuate between rigid and unpredictable responses in decision-making situations, a phenomenon which has been called dysregulation. The aim of this study was to investigate whether schizophrenia patients already display dysregulated behavior at the beginning of their illness. Thirty-two first-episode schizophrenia or schizophreniform patients and 30 healthy controls performed the two-choice prediction task. The decision-making behavior of first-episode patients was shown to be characterized by a high degree of dysregulation accompanied by low metric entropy and a tendency towards increased mutual information. These results indicate that behavioral abnormalities during the two-choice prediction task are already present during the early stages of the illness.

Key Words: Schizophrenia, decision making, two-choice prediction task, dysregulation, entropy.

(*J Nerv Ment Dis* 2008;196: 157–160)

Decision making, the act of making up one's mind, refers to the process of forming preferences, selecting actions, and evaluating outcomes. This act of choosing an action from a number of alternatives if the outcome is uncertain is a complex process that is important in everyday life (Paulus, 2005;Tversky and Kahneman, 1981). Both cognitive and affective functions are involved in the decision-making process. Based on behavioral studies, decision making has been separated into different categories: assessment, i.e., relating a stimulus to outcome probabilities, and evaluation, i.e., optimizing among competing responses and executive processes, such as selecting or updating ongoing response strategies (Kahneman and Tversky, 1984).

In the field of psychiatry and neuroscience, a variety of tests are available that measure decision making. These include the Iowa gambling task (Bechara et al., 1994), the decision-making risk-taking task (Ernst et al., 2002), and the two-choice prediction task (CT) (Paulus et al., 1996). Although no single task can probe all aspects of decision making, we have used the CT to examine the sequential organization of responses during decision making, where the influence of the subject's history of uncertainty or success influences his or her choice of response (Paulus et al., 1996). This task is based on the theory of nonlinear dynamic systems, which is especially suitable for characterizing complex human behavior (Paulus and Braff, 2003).

Dysfunctions in making a decision have been observed in schizophrenia patients in a number of different paradigms (Hutton et al., 2002; Paulus et al., 1999; Sevy et al., 2007). By using the CT, it was possible to show that decision-making behavior is dysregulated in schizophrenia, i.e., characterized by intermittent switching between highly predictable and highly unpredictable actions (Paulus and Braff, 2003).

The aim of this study is to determine whether decision-making dysfunctions are also present in first-episode schizophrenia individuals. Previous studies using the CT only investigated chronic schizophrenia patients under long-term medication. As schizophrenia is a neurodevelopmental disorder, the duration of the illness and the associated treatments may have a profound effect on cognitive dysfunctions, such as concern decision making. We have hypothesized that patients with schizophrenia show deficient measures of decision making. These are characterized by increased dysregulation, even at the onset of the illness. To test this hypothesis, first-episode schizophrenia [or schizophreniform (SZ)] patients and normal comparison subjects completed the CT.

METHODS

Thirty-two first-episode schizophrenic or SZ patients were studied during their first psychotic episode. The patients were recruited from the Psychiatric Services of the Canton of Aargau (Switzerland) between 1999 and 2002. Moreover, we tested 30 comparison subjects (C) who were either hospital employees or individuals recruited via local advertisements. The groups were gender-matched and their ages were similar (see demographics and psychopathology). After the subjects

*University Hospital of Psychiatry, University of Bern, Bern, Switzerland; †Psychiatric Services of Aargau Canton, Department of Research, Brugg, Switzerland; ‡Psychiatric University Hospital of Zurich, Zurich, Switzerland; §Laboratory of Behavioural Neurobiology, Swiss Federal Institute of Technology Zurich, Schwerzenbach, Switzerland; and ‖Laboratory of Biological Dynamics and Theoretical Medicine, University of California, San Diego.

Supported by the Sarasota Opera Benefit through a 2003 NARSAD Young Investigators Award (to K.C.-L.) and the Hartmann-Müller and EMDO Foundations of Zurich, Switzerland, through grants (to F.X.V.).

Send reprint requests to Katja Cattapan-Ludewig, MD, University Hospital of Psychiatry, University of Bern, Murtenstrasse 21, 3010 Bern, Switzerland. E-mail: katja.cattapan@puk.unibe.ch.

ISSN: 0022-3018/08/19602-0157
DOI: 10.1097/NMD.0b013e318162aa1b

had been given a comprehensive description of the study, their written informed consent was obtained. The study protocol and consent forms were reviewed and approved by the Ethics Commission of the Psychiatric Services of the Canton of Aargau. The patients were diagnosed according to ICD-10 and DSM-IV diagnostic criteria, based on DIA-X, a German language diagnostic tool (Wittchen and Pfister, 1997). The exclusion criteria for schizophrenia included substance dependence, major medical disorder, mental retardation, head trauma, and other psychiatric illnesses. The exclusion criteria for the control (C) group consisted of a personal history of psychiatric disorders and psychopharmacological treatment, substance dependence, major medical disorders, mental retardation, head trauma, and psychosis in first-degree relatives. The psychopathological symptoms were measured using the Positive and Negative Syndrome Scale Score [PANSS (Kay et al., 1987); PANSS scores see 5.1 demographics and psychopathology].

Thirty-two first-episode schizophrenia patients performed the CT. Fourteen of these patients were unmedicated. The rest of the patients had been medicated (atypical antipsychotics: $N = 13$; typical antipsychotics: $N = 5$) for less than 2 months.

The purpose of the CT is to quantify decision-making characteristics based on the individuals' sequential response patterns, which result from repeated selections of different alternatives associated with an uncertain outcome. Each subject received computerized instructions. The subject's task is to predict on which side a stimulus (a car on the screen) will appear and select a response (to match up one of 2 figures shown on the screen) accordingly. The outcome is shown for 250 milliseconds after the subject has selected as response. A new trial begins immediately after the car has been displayed. The subject is not given any information about the sequence of the stimulus presentations, i.e., whether the stimulus is presented randomly or in any kind of order. Unbeknownst to the subjects, the location of the car shown is based on the subject's response, i.e., the subject "correctly" predicts the location of the car in 64 trials. The basic measurements consist of the subject's response, the presentation of the car and the latency of the response selection process, i.e., the time from the beginning of the trial to the pressing of the button. For the behavioral analysis, we used nonlinear methods—described elsewhere in detail (Paulus et al., 2001)—to obtain the following key measures:

Dysregulation: Dysregulation quantifies the range of response sequence entropies during the course of an experiment. A high dysregulation value indicates that the response sequences occurring during the experiment are characterized by bothöperseverative tendencies" and highly unpredictable or dynamically "chaotic" strategies.

Metric entropy: Entropy measures the "sequential order" within sequences of responses. Whereas low entropy indicates that the response sequences are highly predictable, high entropy implies highly unpredictable response sequences. Thus, predictability is a collateral measure for the degree to which sequences of responses are based on a consistent internal strategy. However, this measure does not take into account the dependence of the response sequence on external stimuli, which is measured by the cross-mutual information (see below).

Mutual information: Mutual information quantifies the degree to which the previous response predicted the current response and provides a measure of the immediate influence of the past response on the decision in the current trial.

Cross-mutual information: Cross-mutual information quantifies the degree to which the previous location of the stimulus (presentation of the car on the LEFT or RIGHT hand side) is able to predict the current response. As opposed to entropy and mutual information, this measure quantifies the influence of external stimuli on the response sequences.

Switching probability: the probability of using the simple strategy RIGHT – LEFT.

Reaction time: the time between stimulus and response.

We used a t test to compare the ages between the 2 groups and to compare psychopathology between medicated and unmedicated patients. A χ^2 test was applied to compare the frequency of gender within the 2 groups. For analyzing the choice-task data, we applied the one-way between-subjects analysis of variance test (ANOVA) for each separate measure. Measures of behavior were the within-subject factor, whereas group (first-episode schizophrenic/SZ patients vs. healthy Cs) was the between-subject factor. To analyze the statistical correlation between measures of the CT and schizophrenic psychopathology (measured by PANSS), we calculated a Spearman rank correlation within the first-episode schizophrenia (or SZ) patient group.

RESULTS

Demographics and Psychopathology

The patients (SZ) were slightly younger than the Cs. The SZ age mean $\pm$ *SD* 21.9 $\pm$ 3.7, range 17 to 31; the C age mean $\pm$ *SD* 24.2 $\pm$ 4.2, range 19 to 33; $t(60) = 2.33$, $p = 0.002$. There was no statistically significant difference between the gender proportions: SZ: 84.3% men; C: 76.7%; $\chi^2 = 0.59$, NS. The patients displayed an average moderate schizophrenic psychopathology with positive and negative symptoms. PANSS scores mean $\pm$ *SD*: positive symptoms: 17.6 $\pm$ 6.1, negative symptoms: 16.1 $\pm$ 7.4, total score: 71.9 $\pm$ 18.0, general psychopathology: 38.3 $\pm$ 9.7. There were no significant differences on measures of psychopathology (PANSS scores) between unmedicated ($N = 14$) and (temporarily) medicated patients ($N = 18$; data not shown).

Two-choice Prediction Task

The CT statistical details are shown in Table 1. Compared with the C subjects, the schizophrenia patients exhibited significantly more dysregulated behavior, i.e., relatively more highly predictable and highly unpredictable sequences of choices. On average, however, sequences of response generated by the schizophrenia patients were more predictable than those of the C subjects and were therefore characterized by lower metric entropy. The previous response

TABLE 1. Detailed Statistical Results

	Group Effect			
Measure	***F***	***p***	**Mean ± SE (SZ)**	**Mean ± SE (C)**
CT: Schizophrenia, all patients (N = 32; SZ) vs. controls (N = 30; C)				
Dysregulation	5.8	<0.02	1.101 ± 0.050	0.928 ± 0.052
Metric entropy	4.7	<0.03	0.776 ± 0.011	0.810 ± 0.011
Mutual information	3.8	<0.06	0.051 ± 0.009	0.025 ± 0.010
Cross-mutual information	0.4	NS	0.110 ± 0.024	0.090 ± 0.025
Switching probability	12.5	<0.0008	0.557 ± 0.019	0.462 ± 0.019
Reaction time	0.23	NS	1651 ± 123	1563 ± 133
Measure	***F***	***p***	**Mean ± SE (unmed SZ)**	**Mean ± SE (med SZ)**
CT: Unmedicated (N = 14; unmed SZ) vs. medicated schizophrenia patients (N = 18; med SZ)				
Dysregulation	0.5	NS	1.052 ± 0.095	1.140 ± 0.084
Metric entropy	1.1	NS	0.792 ± 0.020	0.764 ± 0.018
Mutual information	1.1	NS	0.037 ± 0.018	0.062 ± 0.016
Cross-mutual information	1.0	NS	0.080 ± 0.040	0.134 ± 0.035
Switching probability	2.8	NS	0.518 ± 0.031	0.587 ± 0.028
Reaction time	0.8	NS	1804 ± 238	1531 ± 210

tended to better predict the current response in the schizophrenia patients than in C subjects, as indicated by higher mutual information.

The degree to which the previous location of the stimulus was able to predict the current response (cross-mutual information) did not differ between the groups. As a specific qualitative characteristic of response, the schizophrenia patients used the switching strategy significantly more often than the Cs (switching probability). No differences were detected between the reaction times of the patients and the Cs. There were no differences between medicated (N = 14) versus unmedicated schizophrenia patients (N = 18).

The choice-task scores of dysregulation, metric entropy, and mutual information were not correlated with different PANSS variables as shown by Spearman rank correlation in first-episode schizophrenia (or SZ) patients. The score of cross mutual information was statistically correlated with the total PANSS score (Spearman R 0.47), negative symptoms (Spearman R 0.52), and anergia (Spearman R 0.45), as well as with general psychopathology (Spearman R 0.39).

DISCUSSION

As shown above in the results section, first-episode patients performing this decision-making test, irrespective of whether they were unmedicated or recently medicated, can be observed to have (a) more dysregulated behavior, (b) a reduced metric entropy, and (c) a tendency towards increased mutual information. As a specific response behavior (d), the patients used the switching strategy more intensely (switching between pushing the right and the left button). This study has supported our main hypothesis that decision-making dysfunctions are already present in first-episode schizophrenia (or SZ) patients.

The schizophrenia pattern of intermittency of fixed and random choice sequences is best conceptualized as a coexistence of highly predictable and highly unpredictable sequences (dysregulation) within the reservoir of behavioral patterns in an individual schizophrenia patient. Although healthy subjects mainly develop their various strategies in performing this test from the previous one (transitions), schizophrenic patients will persist for a long time in strategies, they have chosen and then will abruptly switch from the old to the new strategy. The fact that this decision-making dysfunction can be observed in first-episode schizophrenia (or SZ) patients supports the notion that these dysfunctions are not simply the result of a prolonged disease process or an artifact of an extended treatment with antipsychotic medication. Moreover, the characteristics of these dysfunctions are similar to those previously reported in chronic and long-term medicated schizophrenia patients (Paulus et al., 1996; Paulus et al., 1999; Paulus et al., 2001). The described dysregulation, the range between perseverative tendencies and chaotic strategies, seems to be specific for schizophrenia when compared with other psychiatric disorders such as bipolar disorder, unipolar depression, and panic disorder (Ludewig et al., 2003b; Minassian et al., 2004). In combination, these findings support the notion that dysregulated decision-making behavior may be a potential endophenotypical marker of schizophrenia.

The response sequences of the first-episode schizophrenia (or SZ) patients were characterized by the reduced utilization of possible strategies in attempting to correctly predict the stimulus. This quantitative measure is expressed in terms of metric entropy. Clinically, this behavior would be described as repetitive behavior and ideas and a reduction in the range of alternative strategies.

The group of patients examined within the framework of this study has a tendency towards higher mutual information. In other words, there is a connection between the patient's previous response (Ludewig et al., 2003a) and is less characterized by the feedback the patient has received from the computer in response to the strategy, he or she has chosen.

The triad of high dysregulation, low metric entropy, and (the tendency to) high mutual information as behavior characteristics in the CT were also found in schizophrenia patients who had been ill for a long time, and in particular also in patients suffering from deficit schizophrenia. This is characterized by an intermittent, perseverative, and autistic process, interrupted by infrequent bursts of unpredictable responses. A connection has been suggested between this and Bleuler's concept of autism in schizophrenia. Bleuler introduced the term "autism" in 1911 as the fundamental symptom of schizophrenia to describe a patient's withdrawal into his or her own world of thought and the behavior connected with this withdrawal, such as problems with social interaction (Bleuler, 1911). This concept continues to be applied in modern psychiatric science today (Andreasen, 1999).

First-episode schizophrenia and SZ patients showed a distinct pattern of response sequences characterized by repeated switching behavior. This switching between the right and the left button irrespective of the outcome associated with the response can best be described as response perseveration, which may reflect a combination of pressure to act and inability to generate alternative response sequences. However, future investigations will need to further evaluate the source of this repeated switching behavior, which has also been observed in other first-episode schizophrenia patients using a similar task (RM Bilder, personal communication, December 8, 2006).

CONCLUSION

The main conclusion is that the pattern of the time series of behavioral data using this CT obtained from schizophrenia patients at different stages of their illness is independent of medication status and is stable across the duration of their illness. From other studies, we know that the CT, a very easy task to implement, is reliable (Paulus et al., 2001) and has a high relevance for daily life functions. It thus seems to be a valuable addition to the cognitive task batteries in this field.

REFERENCES

Andreasen NC (1999) A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Arch Gen Psychiatry*. 56:781–787.

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*. 50:7–15.

Ernst M, Bolla K, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, London ED (2002) Decision-making in a risk-taking task: A PET study. *Neuropsychopharmacology*. 26:682–691.

Hutton SB, Murphy FC, Joyce EM, Rogers RD, Cuthbert I, Barnes TR, McKenna PJ, Sahakian BJ, Robbins TW (2002) Decision making deficits in patients with first-episode and chronic schizophrenia. *Schizophr Res*. 55:249–257.

Kahneman D, Tversky A (1984) Choices, values and frames. *Am Psychol*. 39:341–350.

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 13:261–276.

Ludewig K, Paulus MP, Vollenweider FX (2003a) Behavioural dysregulation of decision-making in deficit but not nondeficit schizophrenia patients. *Psychiatry Res*. 119:293–306.

Ludewig S, Paulus MP, Ludewig K, Vollenweider FX (2003b) Decision-making strategies by panic disorder subjects are more sensitive to errors. *J Affect Disord*. 76:183–189.

Minassian A, Paulus MP, Perry W (2004) Increased sensitivity to error during decision-making in bipolar disorder patients with acute mania. *J Affect Disord*. 15;82:203–208.

Paulus MP (2005) Neurobiology of decision-making: Quo vadis? *Brain Res Cogn Brain Res*. 23:2–10.

Paulus MP, Braff DL (2003) Chaos and schizophrenia: Does the method fit the madness? *Biol Psychiatry*. 53:3–11.

Paulus MP, Geyer MA, Braff DL (1996) Use of methods from chaos theory to quantify a fundamental dysfunction in the behavioral organization of schizophrenic patients. *Am J Psychiatry*. 153:714–717.

Paulus MP, Perry W, Braff DL (1999) The nonlinear, complex sequential organization of behavior in schizophrenic patients: Neurocognitive strategies and clinical correlations. *Biol Psychiatry*. 46:662–670.

Paulus MP, Rapaport MH, Braff DL (2001) Trait contributions of complex dysregulated behavioral organization in schizophrenic patients. *Biol Psychiatry*. 49:71–77.

Sevy S, Burdick KE, Visweswaraiah H, Abdelmessih S, Lukin M, Yechiam E, Bechara A (2007) Iowa Gambling Task in schizophrenia: A review and new data in patients with schizophrenia and co-occurring cannabis use disorders. *Schizophr Res*. 92:74–84.

Tversky A, Kahneman D (1981) The framing of decisions and the psychology of choice. *Science*. 211:453–458.

Wittchen HU, Pfister H (1997) *DIA-X Interview*. Frankfurt: Swets Test.

