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Psychophysiological Prodromal Signs of Schizophrenic Relapse: A Pilot Study

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Abstract

Do physiological changes occur shortly prior to psychotic relapse in schizophrenia outpatients? We addressed this question in a group of schizophrenia outpatients by measuring changes in symptoms and changes in activation of the sympathetic nervous system, as indexed by changes in skin conductance level (SCL), on a biweekly basis for between one and two years. All six outpatients exhibited heightened SCL within two weeks prior to relapse or exacerbation, compared to SCL proceeding continued remission. These results shed light on the psychotic relapse process and are consistent with neural diathesis-stress models of schizophrenia.

Keywords

diathesis-stress model; electrodermal activity; prodromal signs; relapse; schizophrenia; skin conductance

1. Introduction

The course of schizophrenia is often marked by periods of relative symptomatic remission punctuated by periods of psychotic symptoms. Phenomenological and behavioral changes

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Conflict of Interest
All authors declare they have no conflicts of interest.

Contributors
MD and AS conceptualized the study design, analyzed the data and prepared the original manuscript. AR collected, organized and helped interpret the data. JV oversaw the quality of the BPRS data collection. KN and KS had broad oversight of the large study in which these patients were participants and they also helped interpret the results and edit the manuscript. All authors commented on the manuscript at various stages of preparation.

are sometimes noticeable within a few days or weeks prior to the appearance of psychotic symptoms (the prodromal period) (Docherty et al., 1978; Herz & Melville, 1980; Subotnik & Nuechterlein, 1988). Common prodromal signs based on self-report include increases in anxiety, tension, somatic concerns, depression, sleep disturbance, social withdrawal, and cognitive inefficiency (see review by Norman & Malla, 1995). The low specificity of these self-reports, however, makes it desirable to search for biological markers of the prodromal period.

According to diathesis-stress models of schizophrenia, stressors that precede exacerbations of psychotic symptoms produce physiological changes that may serve as prodromal signs (Dawson et. al., 1983; Nuechterlein & Dawson, 1984; Walker & Diforio, 1997). One easily measured physiological sign of stress is increased electrodermal activity (EDA). EDA is controlled by the sympathetic nervous system (SNS) (Dawson et al., 2007), is known to increase in response to psychosocial stressors considered key in psychotic relapse in schizophrenia (Tarrier et al., 1979; Tarrier & Barrowclough, 1989), and has been found to increase during exacerbation of symptoms (Dawson et al., 1994).

Which appears first, the heightened EDA or the psychotic symptoms? In a small previous study, EDA arousal was found to be elevated in the weeks prior to a psychotic relapse or exacerbation in 4 out of 5 schizophrenic outpatients (Hazlett et. al., 1997). If this finding proves to be reliable, the hypothesized role of the stress response in triggering psychotic episodes would receive further support. Furthermore, monitoring such transient increases in arousal could potentially indicate when increased intervention (e.g., medication) could potentially prevent an imminent relapse. Therefore, we conducted an intensive prospective longitudinal examination of EDA and symptomatic state on a biweekly basis for up to two years in a group of relatively remitted schizophrenic outpatients. Thus, we were able to determine whether (1) psychotic relapses or exacerbations were preceded by heightened EDA arousal and whether (2) heightened EDA arousal was always followed by psychotic exacerbation or relapse.

2. Method

2.1 Participants

A total of 23 outpatients from the UCLA Aftercare Research Program with a diagnosis of schizophrenia or schizoaffective disorder, mainly schizophrenic, by Research Diagnostic Criteria (Spitzer, et. al., 1978) were recruited. Other inclusionary and exclusionary criteria for participation in the larger study are described by Nuechterlein et al. (1992). Data are reported here for a subset of six patients who were initially in psychotic remission and subsequently satisfied strict symptomatic criteria described in section 2.3, and for whom at least a year of data were obtained. The age, gender, diagnoses, and medication status of all six participants, and the total number of EDA tests completed, are displayed in Table 1.

2.2 Overall design

EDA testing was completed as close as possible to a biweekly schedule during the patients' normally scheduled clinic visits, at which time symptomatic states were also measured with the 24-item version of the Brief Psychiatric Rating Scale (BPRS; Lukoff, et. al., 1986;

Overall & Gorham, 1962). EDA tests that were followed by psychotic relapse/exacerbation ("pre-relapse" test) and tests that were followed by continued symptomatic remission ("pre-remission" test) were then identified based on subsequent changes in the biweekly BPRS.

2.3 Identification of clinical states

The BPRS was administered every two weeks and was used to determine the remitted, psychotic exacerbation and psychotic relapse states. Symptoms were rated on a scale from 1 (not present) to 7 (extremely severe), with ratings of 4 and higher being in the pathological range according to the BPRS anchor points (Ventura et al., 1993). A psychotic exacerbation was defined as an increase from the immediately preceding rating of at least two points in the sum of the three BPRS psychotic items (unusual thought content, conceptual disorganization, and hallucinations), and a rating above 3 on at least one of these items for at least two consecutive biweekly evaluations. A psychotic relapse was defined as an increase from the immediately preceding BPRS rating of at least two points in the sum of the psychotic items in which the score of at least one of the three psychotic items reached 6 or 7. The criteria for exacerbation are consistent with those for a "mild exacerbation" and the criteria for relapse are consistent with those for "relapse" recommended by Nuechterlein et al. (2006).

2.4 Final sample of participants

Of the 23 outpatients, 13 either left the program or did not continue bi-weekly attendance before data could be collected for the full one-year period. Of the remaining 10 participants, two had no remission periods satisfying criteria, one had no relapse or exacerbation, and one was found to have inaccurately reported symptoms. Thus, a total of six patients had both pre-remission and pre-relapse EDA tests.

2.5 Electrodermal tests and measures

EDA was recorded using standard methods (Dawson et al., 2007) during a 5-minute rest period. Two electrodermal measures were obtained: (1) the number of nonspecific skin conductance responses (NS-SCRs) and (2) the mean skin conductance level (SCL). NS-SCRs were defined as the number of responses of at least .05 μSiemens. SCL was defined as the mean of the skin conductance levels recorded at each minute during the rest period.

3. Results

The sums of the 3 BPRS psychotic items, the sums of the 24 BPRS items, the mean skin conductance level (SCL) and the mean rate of nonspecific skin conductance responses (NS-SCRs) were analyzed for each of the 6 participants. For each variable, difference scores were computed between the pre-remission and pre-relapse tests, and Sign Tests were performed on the difference scores.

The mean of the 24 BPRS items were at low levels during both the pre-remission and pre-relapse tests (Figure 1). The mean increased from the pre-relapse period to the relapse period in all patients, whereas there was no significant change from the pre-remission to the remission tests. Likewise, the sums of the 3 psychotic items were relatively low and did not

differ significantly from each other during the pre-remission and pre-relapse tests. There was a significant increase in the psychotic ratings during the relapse period compared to the pre-relapse period ($p = .016$), but not during the remission period compared to the pre-remission period.

Most important, SCL was higher during the pre-relapse test than during the pre-remission test for each of the six patients ($p = .016$). As shown in Figure 2, there is considerable between-patient variability in the absolute values of SCL, but the SCL for each patient was higher during the pre-relapse test than during the pre-remission test. In contrast, the rates of NS-SCRs did not discriminate the two states.

In addition to these tests, three of the six patients had one or more additional psychotic exacerbations less severe than those described above. Of the total of 10 relapses/exacerbations seen across all patients, 8 (80%) were preceded by SCL increases. Thus, SCL showed good sensitivity in prediction of schizophrenic relapse/exacerbation.

On the other hand, specificity was not as high as sensitivity in that several occasions of heightened SCL were not followed by relapses or exacerbations. Four of six patients had other EDA tests besides the pre-relapse tests where SCL was equally high or higher, but without a return of psychotic symptoms. Thus, although relapses or exacerbations were commonly preceded by increases in SCL, such increases were not always followed by relapses or exacerbations.

4. Discussion

Increases in sympathetic nervous system activity, indexed by heightened SCL, occurred reliably in the weeks preceding psychotic relapse and exacerbation, thus replicating and extending findings reported in an independent sample of patients (Hazlett et al., 1997). The present results shed light on the nature of the psychotic relapse process and are consistent with the neural diathesis-stress model of Walker and Diforio (1997) in which the HPA axis activation associated with the stress response, which would be expected to accompany SNS activation, induces dopamine release through the effect of heightened cortisol on dopamine. The results are also consistent with the noradrenalin hypothesis of Yamamoto and Hornykiewcz (2004).

One limitation of this study concerns the relatively small sample. However, the results are statistically significant, and are even more so when combined with those reported previously in an independent sample. Another limitation is that the patients were initially in stable remission, making it possible to define a discrete point of the onset of symptomatic relapse or exacerbation. Defining this time point would be more difficult among patients with persisting symptoms of various degrees (R. Zarate, personal communication, 2009). Research with larger and more heterogeneous samples is needed to test the generality of these results.

An interesting direction for future research is to measure the prodromal signs of sympathetic activation within the ultra high-risk paradigm that identifies distal prodromal signs (Cannon et al., 2007). Such distal signs may identify who is likely to show psychotic symptoms

within 1 to 2 years, whereas the proximal signs may identify when psychotic symptoms are likely to occur within a few weeks.

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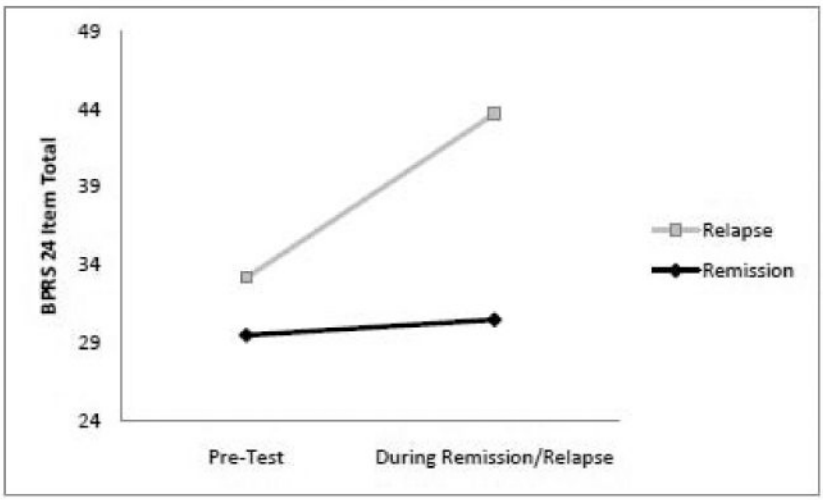

Figure 1.

Mean total scores on the 24 item Brief Psychiatric Rating Scale (BPRS) during the pre-relapse and pre-remission test occasions and during the subsequent relapse and remission occasions. The change from pre-relapse to relapse is significant (p = .016); no other differences are significant. The minimum BPRS score is 24.

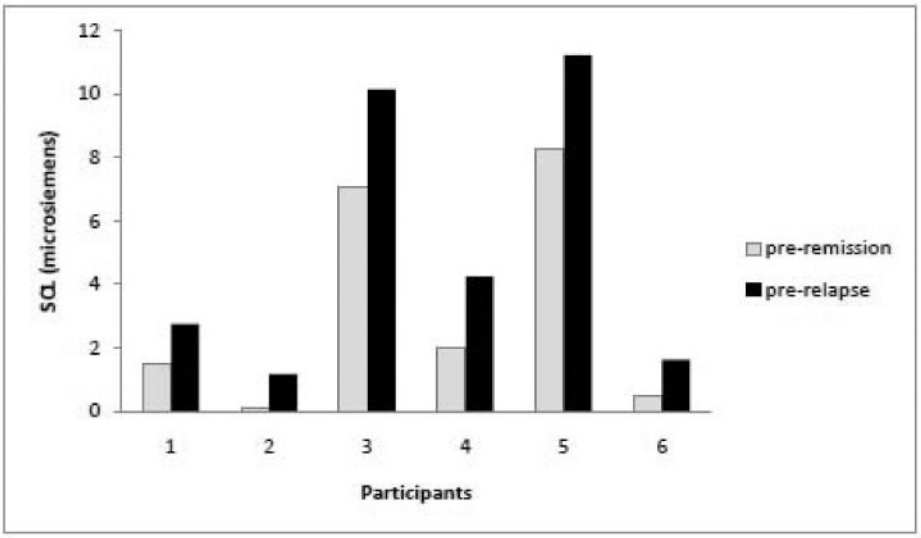

Figure 2.

Mean skin conductance level for each of six patients during the pre-relapse test and the pre-remission test. Patients were in similar remitted states during both the pre-relapse and pre-remission tests but exhibited higher SCL during the pre-relapse tests.

Table 1

Demographic, Diagnosis, Medication Information, and Number of EDA Tests

SZ = Schizophrenia diagnosis

SZAFF = Schizoaffective diagnosis

Participant Number	Gender	Diagnosis	Age at Entry	Number of Tests Completed	Medication Pre-Remission	Medication Pre-Relapse
1	Male	SZ	21.8	24	risperidone 2.0 mg/day	risperidone 2.0 mg/day
2	Female	SZ	25.4	49	risperidone 4.5 mg/day	risperidone 4.5 mg/day
3	Male	SZ	22.8	58	risperidone 6.0 mg/day	risperidone 7.5 mg/day
4	Male	SZ	38.0	72	olanzapine 10.0 mg/day	olanzapine 10.0 mg/day
5	Male	SZ	41.0	30	fluphenazine 10.0 mg/day	fluphenazine 9.0 mg/day
6	Female	SZAFF	41.3	43	olanzapine 10.0 mg/day fluphenazine 6.25 mg/day	olanzapine 50.0 mg/day fluphenazine 10.0 mg/day