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Self-Regulation of Slow Cortical Potentials in Psychiatric Patients: Schizophrenia[1]

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Slow cortical potentials (SCPs) are considered to reflect the regulation of attention resources and cortical excitability in cortical neuronal networks. Impaired attentional functioning, as found in patients with schizophrenic disorders, may covary with impaired SCP regulation. This hypothesis was tested using a self-regulation paradigm. Twelve medicated male schizophrenic inpatients and 12 healthy male controls received continuous feedback of their SCPs, during intervals of 8 s each, by means of a visual stimulus (a stylized rocket) moving horizontally across a TV screen. The position of the feedback stimulus was a linear function of the integrated SCP at each point in time

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during the feedback interval. Subjects were required to increase or reduce negative SCPs (referred to pretrial baseline) depending on the presentation of a discriminative stimulus. The correct response was indicated by the amount of forward movement of the feedback stimulus and by monetary rewards. Schizophrenics participated in 20 sessions (each comprising 110 trials), while controls participated in 5 sessions. Compared with the healthy controls, schizophrenics showed no significant differentiation between negativity increase and negativity suppression during the first sessions. However, in the last 3 sessions, patients achieved differentiation similar to controls, demonstrating the acquisition of SCP control after extensive training.

DESCRIPTOR KEY WORDS: Slow cortical potentials; schizophrenia; biofeedback; instrumental learning; CNV.

Expectancy or preparation for external or internal events is correlated with slow negative variation in the EEG. As such, large-amplitude potentials originate from cortical sources (Rockstroh, Elbert, Canavan, Lutzenberger, & Birbaumer, 1989) and have been labeled "slow cortical potentials" (SCPs) or DC potentials (the latter term refers to the amplification requirements). SCPs such as the "contingent negative variation" (CNV; Walter, Cooper, Aldridge, McCallum, & Winter, 1964) are typically observed in anticipation of signaled responses (for overviews see McCallum, 1988; and Rockstroh, Elbert, Canavan, Lutzenberger, & Birbaumer, 1989).

Evidence suggests that SCPs indicate the regulation of excitability in underlying cortical neuronal tissue (Birbaumer, Elbert, Canavan, & Rockstroh, 1990; Rockstroh et al., 1989). On the neurophysiological level, surface-negative SCPs are known to reflect the depolarization of apical dendritic trees of cortical pyramidal cells. Increased neuronal excitability, i.e., decreased firing thresholds, can be related to a preparatory allocation of energetic-metabolic resources for subsequent cerebral performance. Hence, excitability has to be regulated according to anticipated processing and response demands.

Knowledge obtained from basic SCP research has been applied to the understanding of information processing and behavior disorders in psychiatric patients (for a summary see Timsit-Berthier et al., 1986; Pritchard, 1986). Frequently CNVs in psychiatric patients have been recorded utilizing short anticipatory intervals of 1-2 s. Reduced amplitude of the CNV has recently been reported for various psychiatric groups (e.g., Abraham et al., 1980; Knott & Tecce, 1978; McCallum & Abraham, 1973; Pritchard, 1986; Timsit-Berthier et al., 1984; Verhey, Lamers, & Edmonds, 1984; Verhey, Lamers, Timsit-Berthier, Mantanus, Rousseau, Gerono, Abraham, Mumford, Spencer, & White, 1986). Reduction in CNV amplitude is greater in those schizophrenic patients who display

more positive symptoms. The CNV has been reported to be within normal amplitude ranges, when the schizophrenic patient is in remission, although this is not a consistent finding (Pritchard, 1986). In the chronic stages of schizophrenia nearly every patient demonstrates CNV abnormalities. Pritchard (1986) suggested that the reduced CNV observed in patients with positive symptoms might reflect increased distractibility, whereas the reduction seen in the chronic stages may results from a more general hyporesponsivity of higher CNS structures.

While prestimulus negativity is reduced, postimperative negative shifts are likely to be enhanced in schizophrenics. Unlike healthy subjects, who show a resolution of their negative shifts after the completion of stimulus and/or response processing, schizophrenic patients tend to maintain or even generate an additional negative shift following the imperative stimulus (postimperative negative variation, PINV).

From these results, we infer that schizophrenic patients suffer from impaired regulation of cortical excitability, rather than from a nonspecific inability to generate preparatory brain responses (negative SCPs). Inadequate regulation of excitation manifests in symptoms of attentional resource allocation. A breakdown of attention filters leading to sensory and cognitive overload in demanding situations has often been proposed to underly schizophrenic symptomatology (Broadbent, 1970; Ingvar & Lassen, 1977; Strauss, 1989). Since SCPs reflect regulatory processes mandatory for selection and processing of relevant stimuli, SCP regulation should be impaired in schizophrenic subjects.

In the present study we investigated this hypothesis by examining the ability of SCP self-regulation in schizophrenic patients. By applying biofeedback methods, and instrumental conditioning, SCPs can be modified systematically and behavioral responses can then be observed as dependent variables.

Healthy human subjects can learn to modify their SCPs (i.e., their cortical excitability) "upon command" (or upon discriminative stimuli) in the described paradigm within 1 to 2 training sessions comprising some 100 to 200 feedback trials (for review see Rockstroh et al., 1989). The difference between required negativity and negativity suppression during transfer trials was the most reliable indicator for learned self-regulation of SCPs, since transfer trials can be considered to reflect the transfer of learning of SCPs.

Two questions guided this present study. First, are schizophrenic patients impaired in their ability to control their SCPs comparable to healthy subjects? And, if so, can schizophrenics increase control over SCPs after an extended training period? Answers to these questions might allow assessment of attentional dysfunctions in schizophrenics, and

might eventually open the possibility of using SCP self-regulation as a diagnostic and therapeutic tool (i.e., attentional training).

Moreover, a deficit in the ability to self-regulate attentional processes, i.e., their neurophysiological representation (SCPs), could reflect a permanent pathophysiology of the CNS or a modifiable functional disorder. With permanent and widespread CNS lesions of structures responsible for attentional processing, successful SCP self-regulation, even after extensive training, seems unlikely. Evidence from previous studies with patients suffering from bilateral frontal lobe lesions (Lutzenberger et al., 1980) and temporal lobe epilepsy (Birbaumer, Elbert, Rockstroh, Daum, & Wolf, 1992) indicate the acquisition of some SCP-control. Therefore, the question remains as to whether schizophrenic patients are able to acquire a certain amount of attentional control in a self-regulation paradigm.

METHOD

The experimental procedure employed in this study was similar to the one reported in Schneider, Heimann, Mattes, Lutzenberger, and Birbaumer (1992) and Schneider, et al. (1993).

Subjects

Twelve medicated male schizophrenic inpatients (right-handed according to the Edinburgh Inventory, Oldfield, 1971) and 12 healthy matched male controls participated in the study (Table I lists demographic data for the patient sample). The mean duration of illness was 3 years, with an average of three hospitalizations. A subject's diagnosis of schizophrenia was established by a psychiatrist with the German version of the Structured Clinical Interview in accordance with DSM-III-R, SCID (Wittchen et al., 1987) after an initial DSM-III-R diagnosis was made by the hospital psychiatrist who treats the patient. The subcategory of the individual diagnosis was assigned with the SCID (see Table I). All patients received the diagnosis "schizophrenia" according to DSM-III-R. Illness state of the patients at the onset of biofeedback training was either subacute or chronic. At the beginning of the study the patients' psychopathological assessments showed high impairment in psychosocial adjustment (Global Assessment Scale, Endicott, Spitzer, Fleiss, & Cohen, 1976: $M = 39.6$; $SD = 7.39$), an acute schizophrenic illness (Brief Psychiatric Rating Scale, Overall & Gorham, 1962: $M = 44.7$; $SD = 11.24$), and many negative symptoms (Scale for the Assessment of Negative Symptoms, Andreasen, 1982, Composite Score: $M = 62.0$; $SD = 18.47$). The average daily neuroleptic dosage during training amounted to 1235.23 CPZ units (Davis,

Table I. Description of the Schizophrenic Patients

Patient	Diagnosis (DSM-III-R)	Age	Duration of illness (months)	Frequency of hospitalizations
1	295.90	23	55	5
2	295.94	29	118	8
3	295.94	28	38	4
4	295.91	20	8	1
5	295.94	32	48	1
6	295.91	28	7	2
7	295.31	32	8	1
8	295.94	25	45	3
9	295.91	25	26	3
10	295.91	30	23	2
11	295.91	26	12	3
12	295.91	30	13	1
Mean		27.3	33.4	2.8

1974; *SD* = 485.70). All patients received comparable dosages of the same phenothiazine derivates.

Twelve male volunteers (right-handed according to the Edinburgh Inventory, Oldfield, 1971) served as control subjects. The average age was 27.5 years (*SD* = 4.2; range 20-32 years). Controls were in good health, and none of them reported any previous psychiatric or neurological disorders. Control subjects were required to be free of any medication during and 3 months prior to participation in the study.

Apparatus and Physiological Recording

A computer network (DEC LSI 11/2 and Atari 1040ST) was used to generate experimental stimuli and to store the digitized physiological data. Physiological responses were sampled at 100 Hz. The electroencephalogram (EEG) was recorded from the vertex (C_z, according to the international 10-20 system) using Zak polygraphs with a modified time constant of 30 s and a high-frequency cutoff of 30 Hz. In-Vivo Metrics silver disk electrodes, chlorinated before use, were affixed with Grass EC2 paste (which acted as a conducting agent). The midpoint of a fixed 10 kΩ shunt attached between the subjects earlobes was used as a reference. Electrode sites on the subjects' scalp were cleaned with alcohol, and the upper layers of the skin were abraded with a sterile lancet, in order to reduce impedence to below 5 kΩ. The vertical

electrooculogram (EOG) was recorded via Beckman Ag/AgCl macroelectrodes attached 1 cm above and below the right eye.

Design and Procedure

Continuous visual feedback of SCPs was provided during 8-s trials. The feedback stimulus was the outline of a rocket ship that appeared on a 30 × 40-cm TV-screen placed 2 m in front of the subject, at eye level. The rocket ship moved backward and forward in a horizontal plane through a gap in the center of the screen created by an upper and lower vertical bar. Depending upon which of the two discriminative stimuli appeared on the screen (the letters "A" or "B" together with the feedback stimulus), the subjects were requested to move the rocket out of the gap from left to right. Negative slow potential shifts, referring to baseline level, moved the rocket toward the right where "A" was presented, whereas suppression of negativity or a positive slow potential shift did so when "B" was presented. Assignment of trial type (negativity/positivity) to the discriminative stimuli (the letters "A" or "B") was randomly varied between subjects. Subjects were told that the distance the rocket moved to the right signaled the correct response. They received no information on how to move the rocket. However, they were informed correctly that the task was to change "their brain activity" in one of two opposite directions ("A" or "B").

The success rate of each experimental subject was computed and exchanged into bonus money at the end of each experimental session [on the average $2 and $8 (US) per session].

The position of the rocket was a linear function of the integrated EEG, referring to the mean value of a 1-s pretrial baseline. To equate the difficulty of A-and-B feedback trials, a constant offset of –6 μV was included in the pretrial baseline in order to compensate for increased negativity elicited by anticipated trial onset. Trials were started by the computer only when the pretrial baseline was free of artifacts caused by body or eye movements. In order to avoid spurious EEG recordings due to vertical eye movements, a time-out contingency was realized, which prevented forward excursions of the rocket upon detection of vertical eye movements of the same polarity as the potential responses (for a detailed description see Elbert, Rockstroh, Lutzenberger, & Birbaumer, 1980).

To assess response control in the absence of feedback, "transfer" trials were included, which contained only the letters A or B without feedback. Except for the absence of feedback (rocket), transfer trials were the same as feedback trials. Before the onset of transfer trials subjects were told that their task now consisted of moving an imaginary rocket as re-

quired by the appearance of an "A" or "B." Each experimental session comprised 110 trials of 30 feedback trials presented in alternation with blocks of 20 transfer trials (block 1, 20 transfer trials; block 2, 30 feedback trials; block 3, 10 transfer trials; block 4, 30 feedback trials; block 5, 20 transfer trials). Within each block, A and B trials were presented in pseudorandom order. The interval between the end of one trial and the next pretrial baseline varied randomly between 4 and 12 s. Schizophrenic patients participated in 20 consecutive daily sessions. Healthy controls participated in only 5 sessions because previous experiments have clearly demonstrated SCP control in normals after 2-3 sessions (Birbaumer et al., 1990).

Data Reduction and Analysis

Those trials where the DC shift exceeded 100 μV in the EEG channel or 70 μV in the EOG channel were excluded. Changes in vertical eye movements were assessed in the same way as SCPs. The EOG differentiations in the feedback-and-transfer blocks, which demonstrated significant SCP differentiation, were nonsignificant. SCPs were evaluated by subtracting the mean slow potential observed during the last second of the pretrial period from the mean slow potential observed during the feedback period. For each recording site these scores were then averaged separately for negativity and positivity trials of the feedback-and-transfer blocks. The data were evaluated statistically with ANOVA and post hoc *t*-tests. Greenhouse and Geisser correction for degree of freedom was used when appropriate. If appropriate to the hypothesis a one-tailed *t*-test was conducted. For example, we have hypothesized that without training, schizophrenics cannot perform the self-regulation task as well as control subjects. Only data from the last feedback and transfer block of each session were analyzed as they revealed the SCP control acquired in that session.

RESULTS

SCP Differentiation: Comparison Between Groups

In all sessions, controls achieved a differentiation in SCPs between negativity and positivity trials. This is illustrated in Figure 1, which shows that healthy controls achieved a significant difference between negativity increase and negativity suppression of SCPs within the first 5 training sessions (see Table II for mean values for the different blocks). Results of the paired *t*-tests (one-tailed; replication of earlier presented data) docu-

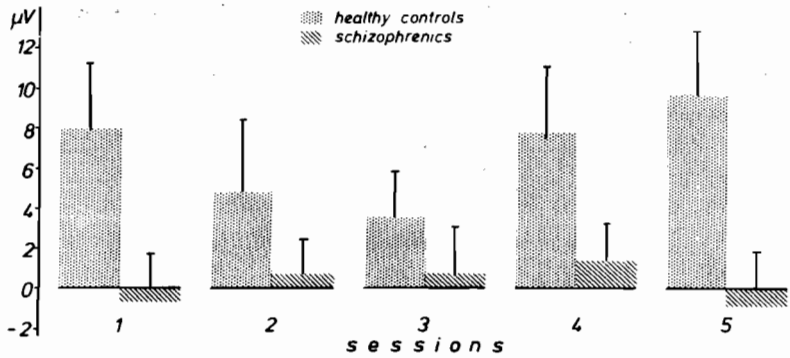

Fig. 1. Each bar represents the mean differentiation of SCPs (in μV ±SE) in the second transfer block between negativity and negativity suppression trials in (a) 12 healthy controls and (b) 12 schizophrenic patients over 5 sessions. Ordinate: Difference in SCPs between negativity and negativity suppression trials.

ment that this differentiation was most pronounced in the second transfer block with 6.66 μV [$t(11) = 3.60$; $p = .002$], and in the second feedback block with 4.28 μV [$t(11) = 2.98$; $p = .005$].

Schizophrenic patients did achieve a mean differentiation of 2.16 μV across the first 5 sessions in the second feedback block [$t(11) = 2.04$; $p = .030$]. In the second transfer block differentiation did not reach significance (0.42 μV).

Data comparison of the first 5 training sessions for schizophrenic patients and controls revealed an impaired performance of schizophrenics under all transfer conditions (see Table II for mean values). This was documented by a four-way ANOVA (Group, Trial Block (feedback, transfer), Session (1-5), and Differentiation (3 repeated measures factors), where the interaction Group × Differentiation reached significance [$F(1,18) = 6.68$; $p = .013$]. The main effect Differentiation [$F(1,18) = 11.31$; $p = .003$] was the result of this interaction.

Figure 2 shows that group difference between Differentiation and Trial Block was more pronounced during transfer conditions than during feedback conditions [Group × Differentiation × Trial Block: $F(1,18) = 3.75$; $p = .069$ — Group × Trial Block: $F(4,72) = 2.79$; $p = .019$].

Closer examination of the second transfer block [with a 3-way ANOVA (Group, Session, Differentiation)] confirmed this finding in that the interaction Group × Differentiation [$F(1,20) = 9.81$; $p = .005$] and the main effect Differentiation reached significance [$F(1,20) = 9.36$; $p = .006$]. Controls exhibited more differentiation than schizophrenics (Figure 1), indicated by the main effect Session [$F(4,80) = 3.91$; $p = .018$].

Table II. Mean Differentiation (+ SE) Between Negativity-and-Negativity Suppression Trials in Microvolts

	Controls	Patients			
	session 1–5	session 1–5	session 6–10	session 11–15	session 16–20
Transfer 1	3.44 ±1.63	0.72 ±1.19	0.50 ±0.74	1.26 ±1.07	–0.24 ±1.56
Feedback 1	3.52 ±2.02	0.25 ±0.71	0.12 ±0.72	0.19 ±1.10	1.14 ±1.38
Feedback 2	4.28 ±1.42	2.16 ±1.06	–0.08 ±0.85	1.41 ±0.75	2.42 ±1.49
Transfer 2	6.66 ±1.85	0.42 ±0.73	–0.45 ±0.89	0.16 ±0.95	2.88 ±1.68

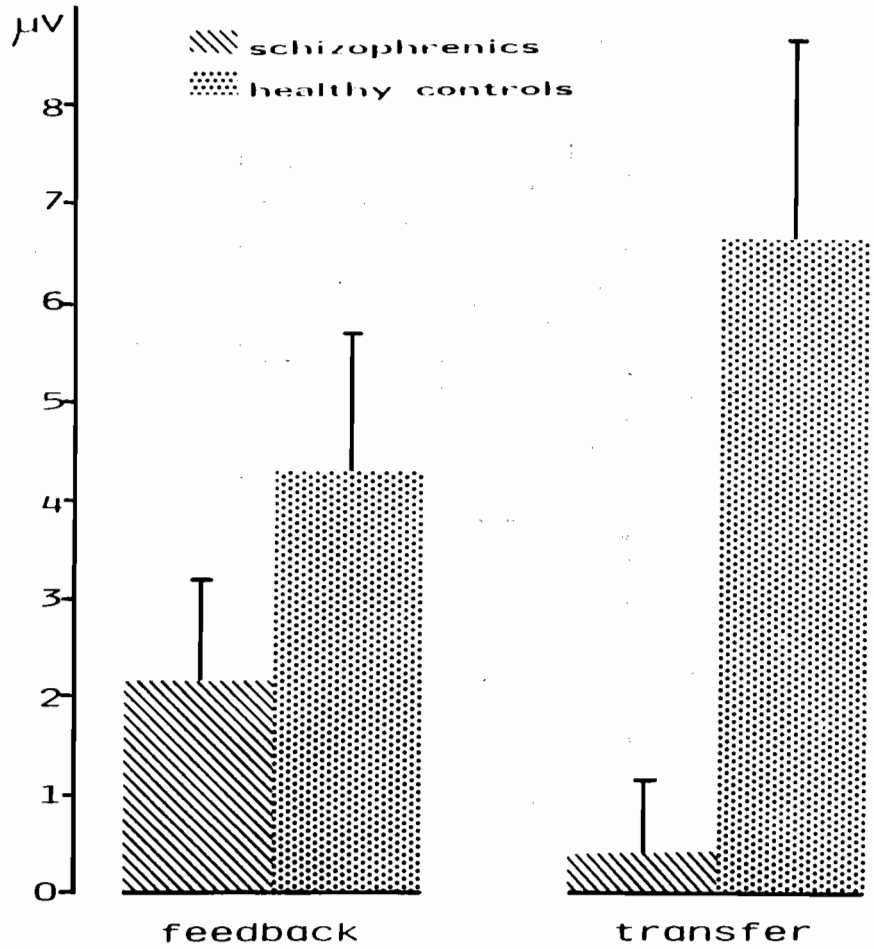

Fig. 2. Mean SCP-differentiation (in μV ±SE) averaged across the first 5 sessions separately for the second feedback (left), and the second transfer block (right) for 12 schizophrenic patients (hatched bars) and 12 healthy controls (dotted bars).

SCP Differentiation in Schizophrenic Patients After Extended Training

Learning of SCP control across the 20 sessions in schizophrenic patients was evaluated by a 3-way ANOVA for repeated measures [Trial Block (feedback, transfer), Session (3-5, 6-8, 9-11, 12-14, 15-17, 18-20) and Differentiation]. The main effects Differentiation [$F(1,11) = 8.22$; $p = .015$]

and Trial Block [$F(1,11) = 6.44$; $p = .028$] reached significance. Session had an F-value of 1.67 ($df = 5,55$; $p > .10$), Session × Differentiation [$F(5,55) = 1.98$; $p = .096$] and Trial Block × Differentiation [$F(1,11) = 2.71$; $p > .10$].

With t-tests (repeated measures) we compared the averaged differentiations of sessions 1-5, 6-10, 11-15, and 18-20. During the first few sessions patients demonstrated a small SCP differentiation of 2.16 μV [$t(11) = 2.04$; $p = .030$], which, however, was not maintained in the second feedback block. Only during sessions 18-20 did patients once more achieve significant differentiations [3.83 μV; $t(11) = 2.16$; $p = .026$].

Across the 20 sessions the mean SCP differentiation in schizophrenic patients increased from 0.42 μV (n.s.) in the first 5 sessions (averaged across all trials of the second transfer block) to 4.13 μV [$t(11) = 2.13$; $p = .028$] in sessions 18 to 20 (see Table II for mean values and Figure 3). No significant SCP differentiations were observed for sessions 6 to 10 and 11 to 15.

Psychopathological Status and SCP Differentiation

Learning success, i.e., the mean difference between required negativity increase and negativity suppression averaged across the last 3 sessions, correlated negatively with (a) symptomatology at the beginning of the study (BPRS: $r = -.51$; $p = < .1$; SANS: $r = -.38$; n.s.; GAS: $r = .47$; $p < .1$); (b) history of illness (duration of illness in months: $r = -.25$; n.s.); and (c) number of hospitalizations ($r = -.58$; $p = < .05$). On the other hand, the patients' daily neuroleptic dosage did not correlate with SCP differentiation (for the last transfer block: $r = -.02$).

DISCUSSION

Previous studies have established that healthy human subjects can learn to modify their slow potentials upon presentation of discriminative stimuli (Rockstroh et al., 1989). Thus far, however, learning was only evaluated in 2 sessions. In the present study, healthy controls demonstrated reliable control in 5 sessions, i.e., significant differentiation between negativity increase and negativity suppression. Thus, our findings replicate and extend those reported previously (Roberts, Birbaumer, Lutzenberger, Elbert, & Rockstroh, 1989).

Compared to healthy controls, schizophrenic patients were less efficient in SCP self-regulation, showing very little control over SCPs at the beginning of the training program. This was especially evident in transfer

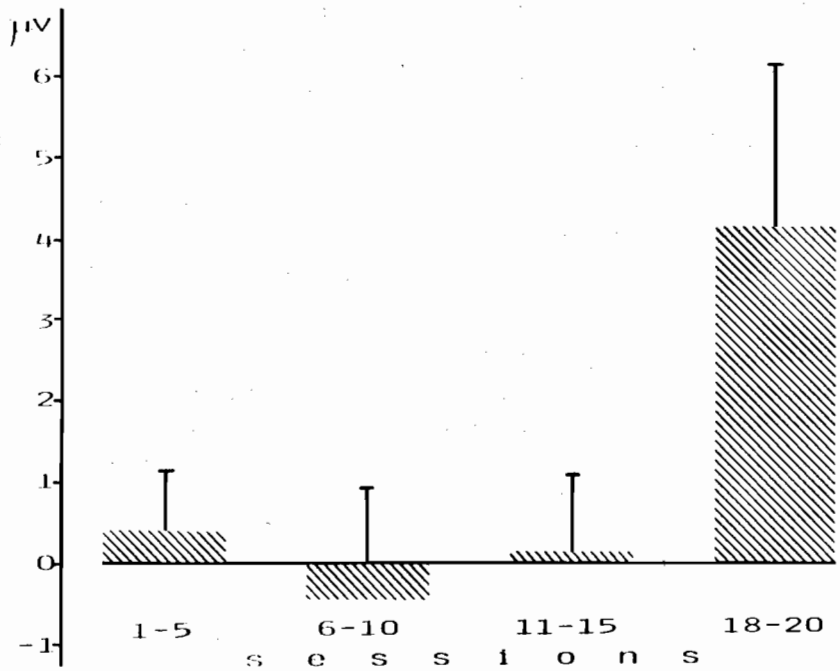

Fig. 3. Mean differentiation between negativity and negativity suppression trials of SCPs (in µV ±SE) in the second transfer block in 12 schizophrenic patients across the 20 sessions. SCPs are averaged across successive sessions.

conditions that lacked immediate continuous feedback of SCPs. The difference between required negativity increase and negativity suppression during transfer trials was the most important indicator for *learned* self-regulation of SCPs, since transfer trials can be considered to reflect the transfer of learning and generalization of SCPs.

These findings support the hypothesis that schizophrenic patients may suffer from an altered regulation of their cortical excitability, which may express itself — among other problems — in attentional deficits. A comparable failure to systematically modify SCPs in the SCP self-regulation was observed in subjects at risk for schizophrenia (Elbert, Lutzenberger, Rockstroh, & Birbaumer, 1983), in neurological patients with bilateral frontal lobe lesions (Lutzenberger et al., 1980), and in children with attentional dysfunctions (Rockstroh et al., 1990). It is tempting to speculate that these similarities point to a common factor of altered SCP regulation, or to an

impaired ability to generalize acquired attentional control to situations without immediate feedback. The above-mentioned populations frequently exhibit signs of dysfunctional frontal lobe function. Since prefrontal regions are intimately involved in the regulation of selective attention and the timing of behavior, particular in delayed response tasks (Fuster, 1989), the regulatory deficit observed in schizophrenics may reflect — at least in part — a failure in prefrontal functioning.

What are the factors that contribute to the poor performance of schizophrenic patients on the SCP-control task? Psychiatric ratings indicated that the more severe the patient's psychopathology, the longer his/her duration of illness, and the more often he/she was hospitalized, the worse he/she performed on the SCP self-regulation task.

There was no clear relationship between medication and performance on the SCP self-regulation task. It is possible that the observed group effect may be more related to the use of phenothiazine than to schizophrenia. However, it is nearly impossible to study this problem in detail: neither the analysis of CPZ-equivalents nor blood plasma concentration levels will be a sufficient answer, but we have some indirect signs of the minor relevance of the medication. Schizophrenics are able to differentiate SCPs upon command after excessive training under medication. Alcohol-dependent patients also exhibit the same deficits even after withdrawal (Schneider, Elbert et al., 1993) without neuroleptics.

We are aware of the possibility of a nonspecific effect, in that the patient's ability to concentrate on the task might be worse the more severe his actual state of illness. The same may be true for findings of a reduced CNV under two-stimuli conditions, where the CNV normalizes again with improvement of the symptomatology.

The question remains whether motivational factors in a learning paradigm where healthy controls are compared with schizophrenic patients are a sufficient explanation for the observed differences. Literature on information processing in schizophrenics (Neale & Oltmanns, 1980) suggests that these patients exhibit a deficit in controlled attentional processing even in situations where personal gratification for correct processing is very high. According to the daily interviews (after each session and a longer one at the end of training), we have no doubt that patients' motivation to participate was very high — greater than that of controls. The patients (and the control subjects) participated voluntarily and expressed hope to improve their condition with the training.

None of the participating subjects dropped out of training, again indicating a stabile motivational situation. Schizophrenic patients had no trouble understanding the instructions. This was secured before each session during 6 practice trials. Their perfect comprehension of instruction

and task condition is also documented by their significant control of SCP differentiation *with* feedback. As in patients with frontal lobe dysfunctions it is the *transfer of training* in which the underlying disorder expresses itself. Since the prefrontal cortex is considered to be essential for SCP regulation (Skinner & Yingling, 1977; Birbaumer et al., 1990) the SCP-regulation task may be suited to uncover such impairments.

With extended training, schizophrenic patients were able to learn to modify their SCPs systematically. By comparison, depressive patients, like healthy controls, already possessed this ability at the beginning of training despite low motivational initial conditions (Schneider, Heimann et al., 1992). Alcohol dependent patients also exhibited the same deficits as schizophrenics even after withdrawal: they do not differentiate in the self-regulation task (Schneider, Elbert et al., 1993).

Whether patients may profit from biofeedback training with respect to attentional functioning remains an open question for further research. Considering the fact that surface negative SCPs of the cerebral cortex reflect preparatory attentional processes, the biofeedback training of SCP self-regulation may be utilized both for the assessment of attentional dysfunctions as well as for the training of attentive behavior in schizophrenic patients.

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