Normal sustained effects of selective attention are absent in schizophrenic patients withdrawn from medication

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Abstract

Sustained attentional deficits have been widely reported in groups of medicated schizophrenic patients, but less is known about sequential attentional processes in patients withdrawn from medication. The attentional performance of 12 medication-withdrawn schizophrenic outpatients was compared with that of 16 matched normal volunteers on a Stroop negative priming task. This task allowed examination of both within-trial and between-trial attentional effects. Compared with the volunteers, the medication-withdrawn schizophrenic patients showed normal within-trial attentional effects as measured by standard Stroop interference and facilitation. Across trials, however, the schizophrenics exhibited reduced negative priming compared with the volunteers and in some cases a complete reversal of sustained inhibitory processes. The findings suggest that a normal inhibitory tag occurred during initial selection in the patient group, but it did not influence a subsequent act of selection as was the case for the normal volunteers. Either inhibition decayed at an abnormally fast rate in the patient group or a separate facilitatory tag dominated. In either case, priming effects linked to attentional selection were clearly abnormal in the medication-withdrawn patient group.

Keywords: Neuropsychology; Negative priming; Stroop Task; Reaction time

1. Introduction

Inefficient inhibitory mechanisms have long been considered a hallmark of schizophrenia (Bleuler, 1911; Kraepelin, 1919; Nuechterlein and Dawson, 1984). While some theorists have proposed that persons with schizophrenia are unable to filter out and inhibit irrelevant stimuli at the sensory level (McGhie and Chapman, 1961; Chapman and McGhie, 1963; Chapman, 1966; Lawson et al., 1967), others have proposed that the deficit in inhibitory processes actually occurs at a later stage of processing (Straube and Gerner, 1979; Hemsley and Richardson, 1980). Multiple tasks have been used throughout the years to assess selective attention capabilities in persons with schizophrenia including the following: dichotic listening (Payne et al., 1970; Wishner and Wahl, 1974; Wahl, 1976); Stroop word interference task (Carter et al., 1992,
1993; Cohen and Servan-Schreiber, 1992); signal detection tasks (Pfefferbaum et al., 1980; Grillon et al., 1991; Ford et al., 1994); and negative priming tasks (Beech et al., 1989; LaPlante et al., 1992).

While some cognitive theorists propose that selective inhibitory processes operate passively (Neely, 1977), others suggest that active inhibitory processes are engaged to reduce the level of processing of a distractor (Tipper, 1985; Tipper and Cranston, 1985). Tipper proposes that these active inhibitory mechanisms produce an effect called 'negative priming'. Negative priming is a slowed reaction time that occurs when a distractor from a previous trial (trial 'n-1') becomes the target on the subsequent trial (trial 'n'). Negative priming is believed to occur when efficient inhibitory processes have suppressed the distractor on trial n-1, thus making the distractor less available on trial n when it becomes the target. If the distractor has not been suppressed or inhibited on trial n-1, then it should be readily available for processing on the next trial and no negative priming would be observed.

There is substantial evidence in the cognitive literature that negative priming is a sensitive measure of inhibition of a previous distractor (Tipper, 1985; Tipper and Cranston, 1985). If distractor information is actively inhibited during the selection of a target, then the previous distractor should be less available on subsequent trials. It is this reduced availability measured through slowed reaction time that has been coined 'negative priming' (Tipper, 1985). Since negative priming is believed to be a product of efficient selective attentional mechanisms, it should be a powerful tool for examining selective attention in persons with schizophrenia. In particular, negative priming tasks provide an opportunity to test sustained effects of attentional processes across experimental trials.

Dalyrymple-Alford and Budayr (1966) were the first to use the Stroop color-naming task (Stroop, 1935) in a negative priming procedure to examine inhibition in young healthy subjects. Using a whole-list procedure, they found that reaction times were slowed on a proportion of trials in which the ink color to be named was preceded by the corresponding color name. Thus, reaction time to name the ink color of the word BLUE written in red ink was slow when it was preceded by the word RED written in green ink. Their explanation was that the subjects had to suppress the color name RED in order to say the ink color green on trial n-1. When the next response required the subject to access the ink color red, they were slowed due to its suppression on the previous trial. Neill (1977) subsequently replicated this effect in a computerized version of the Stroop task with response time recorded on each trial. He later replicated this result for both vocal and manual response modalities (Neill and Westberry, 1987).

Beech et al. (1989) investigated negative priming in medicated schizophrenic patients with the computerized trial by trial Stroop task. Their results showed that the schizophrenic group exhibited reduced negative priming in contrast to a non-psychotic psychiatric comparison group. These results were consistent with reduced inhibitory control in medicated subjects with schizophrenia. LaPlante et al. (1992) also used Stroop stimuli to investigate negative priming in medicated schizophrenic patients. Using a manual response design, they tested 18 medicated schizophrenic patients and found a lack of negative priming among patients with both negative and positive symptomatology. LaPlante et al. proposed that while the schizophrenic group displayed a level of within-trial interference comparable to that found in the control group, they lacked a 'higher level of inhibition necessary to produce a distractor-suppression effect'. Similar patterns have also been found in negative priming studies of subjects who scored high on a schizotypy scale with the interesting exception that in some cases the high schizotypal group not only failed to demonstrate negative priming, but instead showed the reverse pattern of facilitation (Beech et al., 1989; Claridge et al., 1992). Facilitation occurs when the reaction time to trial 'n' is actually faster for a target that was previously a distractor than the reaction time to pairs in which there is no relationship between either ink color or color name.

One of the goals of the present study was to test whether chronic schizophrenic patients withdrawn from neuroleptic medication would exhibit the same negative priming effects as shown in previous
studies that tested medicated schizophrenic patients. In general, earlier studies have shown that neuroleptic treatment facilitates the rate of processing in persons with schizophrenia while reducing the intrusion of irrelevant distractors (Pigache and Norris, 1973; Oltmanns et al., 1978; Nestor et al., 1991). If neuroleptic medication enhances cognitive processing and reduces distractibility on attentional tasks (Spohn and Strauss, 1989; Nestor et al., 1991), it is reasonable to hypothesize that schizophrenic patients withdrawn from medication might perform abnormally on negative priming tasks. In addition, increased Stroop interference within a trial has been associated with reduced control of selective attention processes (Tzelgov et al., 1990). Increased Stroop interference has also been demonstrated in some schizophrenic patients (Wapner and Krus, 1960; Grand et al., 1975; Abramczyk et al., 1983; Wysocki and Sweet, 1985; Carter et al., 1993). Thus, a second hypothesis was that an inverse correlation would be found between interference and negative priming. If the ability to efficiently inhibit or suppress irrelevant information on trial n-1 is correlated with negative priming on trial n (Tipper, 1985; Tipper and Cranston, 1985), then a deficit in suppressing irrelevant information among the schizophrenic subjects may result in reduced negative priming effects.

2. Methods

2.1. Subjects

The schizophrenic group consisted of 12 outpatient participants who were part of an investigational drug study at the University of California Medical Center in Sacramento. Patients enrolled in the investigational drug study were outpatients who were typically seeking an antipsychotic medication with fewer side effects. All patients met diagnostic criteria for chronic schizophrenia according to DSM-III-R (American Psychiatric Association, 1987). Ten of the 12 patients were classified as paranoid subtype (characterized by one or more systematized delusions or hallucinations around a single theme and an absence of incoherence, marked loosening of associations, flat or grossly inappropriate affect, catatonic or grossly disorganized behavior), while the remaining two were classified as having the undifferentiated subtype (prominent delusions, hallucinations, incoherence, or grossly disorganized behavior while not meeting criteria for paranoid, catatonic, or disorganized subtype). All patients had been withdrawn from antipsychotic medication for at least 2 weeks before testing (Spohn and Strauss, 1989). None of the patients were neuroleptically naive. In addition, no anticholinergic medications or short-acting benzodiazepines had been taken 48 h before study. All patients were chronic and had been ill for a mean period of 13.13 years (SD = 7.6). Sixteen normal subjects were tested. Twelve of the normal subjects were recruited through newspaper advertisements or through local community colleges; they had no history of mental disorder and no first degree family history of mental illness. The remaining four normal subjects were recruited from a VA subject control pool. All the VA controls had also been screened for a history of mental illness. Controls and patients were screened with a semistructured psychiatric interview based on the Structured Clinical Interview for DSM-III-R (Spitzer and Williams, 1986) both upon entry into the study and on the day of cognitive testing (available upon request). Sixteen controls were matched to the schizophrenic subjects on age (patients: mean = 37.58 years, SD = 9.78; control subjects: mean = 40.8 years, SD = 8.81) and years of parent's education (to match approximately for socioeconomic status; patients: mean = 12 years, SD = 2.3; control subjects: mean = 13.38 years, SD = 4.3). All subjects were right-handed. The schizophrenic group included 10 males and 2 females, while the control group comprised 9 males and 7 females. Both patients and controls were paid for their participation, and all gave informed consent.

2.2. Apparatus

The experiment was programmed on an IBM-compatible computer using Micro Experimental Laboratory version 2.0. Stroop stimuli were presented on an Everex color monitor with the presentation of the stimuli controlled by an Everex 386si microcomputer. Response timing was to 1-
ms resolution and was controlled by the 8253 chip. Stimulus timing was tied to the vertical sync pulse. All reaction times were recorded with a Gerbrands voice-operated relay interfaced with the computer and monitored through the gameport.

2.3. Stimuli

Stimuli were presented in one of four colors: red, blue, yellow, and green and consisted of standard DOS characters. The within-trial incongruent stimuli consisted of the four color names printed in one of the three remaining colors. The within-trial congruent stimuli consisted of color names printed in the corresponding ink color. Within-trial neutral stimuli consisted of animal names (TIGER, BEAR, MONKEY, and DOG) printed in one of the four colors of inks and strings of X's printed in one of the four colors of ink. Within-trial Stroop interference was calculated by subtracting the reaction time on all the neutral trials from all the incongruent trials. Within-trial Stroop facilitation was calculated by subtracting all congruent trials from all neutral trials. Within-trial Stroop effects were calculated across all trials.

Sequential relations using Stroop stimuli were evaluated by comparing reaction times on the second trial of related pairs (pairs in which the color name on trial n-1 corresponds to the color ink on trial n); for example, RED printed in blue ink followed by GREEN printed in red ink from the second trial in unrelated pairs. Unrelated pairs are pairs of trials in which there is no congruence of any color; for example, RED printed in blue ink followed by GREEN printed in yellow ink or TIGER printed in yellow followed by BLUE written in red. Negative priming was calculated by subtracting the reaction time of the second trial of an unrelated pair from the second trial of a related pair. The first trial (trial n-1) within the pair was not analyzed for negative priming. Within each block, 25% of the trials were related, 25% were unrelated, and 50% were fillers. Four hundred trials were presented, with six experimental blocks (each containing 60 trials) and two practice blocks (each containing 20 trials).

2.4. Procedure

Subjects were instructed to say aloud the ink color that the words were printed in while ignoring the word itself. Subjects were given instructions which discouraged a speed/accuracy tradeoff in that they were told to respond as quickly as they could while making as few errors as possible. Each trial began with a blank screen after which the stimulus appeared at the center of the screen. The onset of the subject's voice triggered the voice-operated relay switch (recorded by the computer in ms) and terminated the stimulus display on the screen. The experimenter then typed in the first letter of the subject's response which allowed for an accuracy analysis of the response. The experimenter's response initiated the subsequent trial. After 20 practice trials, subjects were presented with three blocks of 60 trials each. After the first three experimental blocks, a 2-min break was given followed by a second practice block and the final three experimental blocks. All experimental blocks were counterbalanced for order using a latin square design.

Negative priming was calculated by subtracting the reaction times on the second trial or trial n of unrelated pairs (pairs in which there is no congruence of any color) from the second trial or trial n of negative priming pairs (pairs in which the color name on trial n-1 corresponds to the color ink on trial n). Within-trial Stroop interference was calculated by subtracting reaction time on all neutral trials from all incongruent trials. Within-trial Stroop facilitation was calculated by subtracting reaction time on all congruent trials from all neutral trials.

3. Results

Each subject's data were first trimmed for outliers by standard procedures. The mean response time and SD were calculated for each subject and reaction times were eliminated if they were 3 SDs above the mean reaction time for that subject or below 150 ms. The number of trials eliminated by this measure ranged from 0 to 12 and averaged <1% overall. New mean reaction times for each subject were then calculated for each cell of the design. Only correct responses were included in the analysis of reaction times.

Analysis of variance (ANOVA) procedures for
mixed design were used to analyze the data in two separate analyses. This design was chosen over a single ANOVA because the study did not include a neutral condition on trials used to calculate negative priming, thus making it impossible to look at the relationship between Stroop interference and negative priming with a single analysis. The first analysis evaluated negative priming effects with group (schizophrenic vs. control) as a between-subject factor and word-type pair (negative priming vs. neutral pair) as a within-subject factor. The second analysis evaluated within-trial Stroop effects with group as a between-subject factor and consistency between word and color (congruent, neutral, incongruent) as a within-subject factor.

3.1. Between-trial effects (negative priming)

Fig. 1 displays the mean negative priming scores for each group. The schizophrenic group had significantly longer response times than the control group ($F = 7.98$, $df = 1.26$, $P < 0.01$). The main effect of word type was not significant, but more importantly, there was a significant interaction between word type and group ($F = 5.55$, $df = 1.26$, $P < 0.03$). Planned comparisons demonstrated that response times for control subjects were faster on neutral pairs than on negative priming trial pairs (776 ms vs. 814 ms). There was a 38-ms negative priming effect that was similar in magnitude to that of healthy normal subjects reported in the literature ($t = 2.35$, $df = 26$, $P < 0.05$). No significant difference was found for the schizophrenic group. If anything, the response in the schizophrenic group was in the opposite direction from that in the control group (a 29-ms faster response for negative priming pairs than neutral pairs).

3.2. Within-trial effects

Table 1 displays the mean reaction time for each group for each condition. While the means for schizophrenic patients were overall longer ($F = 13.36$, $df = 1.26$, $P < 0.001$), and there was a significant consistency effect ($F = 23.60$, $df = 2.52$, $P < 0.001$), there was no significant interaction between group and consistency ($F = 0.21$, $df = 2.52$, $F < 1$). This lack of interaction between group and consistency shows that schizophrenic patients withdrawn from medication did not differ from matched controls on either within-trial Stroop facilitation or within-trial Stroop interference. Although there was about twice the magnitude of facilitation for schizophrenic patients than for controls in the means, this difference did not reach significant levels.

3.3. Within-trial vs. between-trial effects

Because one of our hypotheses was that an inverse correlation would be found between interference and negative priming, we ran a simple correlation between Stroop interference and negative priming across all subjects. Our findings showed a lack of correlation between within-trial inhibition and between-trial negative priming effects ($r = 0.0$, $F < 1$).

3.4. Error analysis

Errors were analyzed with same design. The results showed that while the schizophrenic patients' mean error rate was 10%, the controls only exhibited 4% errors. While schizophrenic patients made significantly more errors than the age-matched controls ($F = 5.18$, $df = 1.26$, $P < 0.05$), there was no evidence of a speed-accuracy tradeoff. There was a positive correlation between reaction time and errors ($r = 0.458$). Subjects with
Table 1

<table>
<thead>
<tr>
<th>Word/color consistency</th>
<th>Schizophrenic patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Congruent</td>
<td>Neutral</td>
</tr>
<tr>
<td>Congruent</td>
<td>861</td>
<td>911</td>
</tr>
<tr>
<td>Neutral</td>
<td>668</td>
<td>696</td>
</tr>
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faster reaction times made fewer errors than those with longer reaction times.

4. Discussion

4.1. Negative priming

The results of the present study are consistent with the literature demonstrating that persons with schizophrenia have attentional processes that operate differently from those of healthy control subjects (Chapman, 1966; Hemsley and Richardson, 1980; Nuechterlein and Dawson, 1984). If negative priming is a manifestation of selective inhibition that carries over from trial n-1 to trial n, then the absence of negative priming among the schizophrenic group supports the hypothesis that selective attention is degraded or the product of selection dissipates over time. Cognitive studies with healthy young normal subjects have shown that negative priming occurs when a previously presented distractor on trial n-1 becomes the target on trial n (Tipper, 1985; Tipper and Cranston, 1985). Tipper (1985) proposed that the active inhibition of the distractor on trial n-1 makes the internal representation of the distractor less available on trial n, which then produces costs in response time or negative priming. The medication-withdrawn schizophrenic group in the present study showed a total lack of negative priming. This lack of negative priming was present in the face of normal within-trial Stroop interference effects. The dissociation between within-trial and between-trial performance is consistent with the interpretation that some selective attentional processes were intact while others were dysfunctional. Alternatively, the strength of the within-trial inhibition in patients with schizophrenia may dissipate from trial n-1 to trial n. In other words, there may be a memory loss of what was inhibited on the previous trial.

The present study not only revealed a lack of negative priming in the medication-withdrawn schizophrenic patients, but a subset of the patients showed facilitation on negative priming trials. If the inhibition of the color name on trial n-1 were attenuated or lost between trials in the schizophrenic group (producing the lack of negative priming), what would be the mechanism that primes the ink color on trial n? One explanation is that the schizophrenic subjects simply do not process the distractor fully on trial n-1. This hypothesis has its problems. If the stimulus were not processed fully on trial n-1, one would expect to see smaller within-trial Stroop interference effects. This hypothesis was not borne out in the present study. The within-trial Stroop interference did not differ significantly between schizophrenic and control subjects, and both groups showed significant interference within trials. Another possible explanation is that the semantic coding of the color name was attenuated or lost over time in the presence of sustained perceptual color representation. This perceptual code could then positively prime the subsequent color, producing facilitation. Any color word could produce a dual representation associated with separate neural systems (e.g., word semantics and color), with one system being more affected in schizophrenia than the other. The very fact that the color name affects response time to name the ink is consistent with an interaction between semantic and perceptual codes during a trial.

The present study was not the first to report facilitation on negative priming trials in a subset of psychiatric patients. Beech et al. (1989) also found facilitation on negative priming trials in a group of
subjects who scored high on the schizotypy scale. While there is debate about whether schizotypal personality disorder is part of the schizophrenia continuum, this finding is of interest as patients with schizotypal personality disorder do share some symptoms with schizophrenic patients. Some researchers have argued that schizotypal personality is part of the schizophrenia spectrum (Siever et al., 1993). Like the schizophrenic patients in this study, the schizotypal subjects in the study of Beech et al. were not taking neuroleptic medication. If neuroleptic medication ameliorates selective attentional processes (Picache and Norris, 1973; Olmanns et al., 1978; Spohn and Strauss, 1989; Nestor et al., 1991), then it is possible that the lack of between-trial negative priming reported in medicated patients may actually reflect an improvement in attentional processes when normal inhibitory tags are weakened over time. This raises possibilities about the role of neuroleptics in sustained effects of attentional processing and suggests directions for further research.

4.2. Within-trial Stroop interference

The present study failed to replicate earlier studies which found increased within-trial Stroop interference in schizophrenic patients (Wapner and Krus, 1960; Grand et al., 1975; Abramczyk et al., 1983; Wysocki and Sweet, 1985). While most of the above studies reported increased Stroop interference across all subtypes of schizophrenic patients, one study found a dissociation in Stroop task performance between subtypes of schizophrenic patients (Carter et al., 1993). Carter et al. found a dissociation between undifferentiated patients and paranoid patients on measures of facilitation and interference. Compared with healthy subjects, the patients classified as paranoid showed increased within-trial Stroop interference, while the undifferentiated patients did not. Our patient group consisted of 10 patients who fit the paranoid subtype. Their within-trial Stroop interference did not show a significant difference from that of the controls.

A possibility for the disparity between our findings and the earlier results of Carter et al. is that we had a higher percentage of incongruent trials in our negative priming Stroop task. It has been shown that with an increased frequency of incongruent trials, within-trial Stroop interference is actually reduced (Logan and Zbrodoff, 1979). This is presumably due to an expectancy bias. If this is the case, however, one should expect to see equivalent reductions in Stroop interference for both the controls and the patients.

4.3. Within-trial Stroop facilitation

While our results demonstrated a lack of negative priming, the findings did not reveal any significant differences in within-trial Stroop facilitation. Earlier studies have shown a dissociation between within-trial Stroop interference and within-trial Stroop facilitation with regard to clinical subtypes of schizophrenia (Carter et al., 1992). Carter et al. found increased within-trial Stroop facilitation in a subgroup of undifferentiated schizophrenic patients when compared with healthy controls. Our patient sample had a very small number of schizophrenic subjects who were classified as undifferentiated (n = 2). Because of the small number, it was not possible to analyze the data separately. It should be noted, however, that both patients who were classified as undifferentiated did exhibit facilitation on the between-trial Stroop negative priming.

4.4. Summary

The absence of negative priming in the present group of schizophrenic patients withdrawn from neuroleptic medication is consistent with previous studies showing that groups of medicated schizophrenic patients have reduced negative priming effects. The reduction or absence of negative priming has been interpreted as abnormal inhibition in selectively attending to a stimulus. Healthy normal subjects are slowed when a previously inhibited color word appears as the color to be reported on the next trial. Schizophrenic groups withdrawn from neuroleptic medication showed a reduction, if not a complete loss and reversal of negative priming. This finding emerged in the context of normal within-trial Stroop performance, both for interference and facilitation. It is uncertain why the present group of schizophrenic patients did not show abnormal within-trial Stroop interference, but it is clear that abnormal priming
was not related to abnormal inhibition of the color word at the time of selection on the previous trial. This finding cannot be explained by general slowing in the schizophrenic patients as negative priming is a performance deficit of slowed reaction time that is associated with normal cognitive functioning (Neill et al., 1992). This finding is more consistent with a rapidly decaying trace of an inhibitory tag. The fact that inhibition had occurred was lost in the interstimulus interval. If this model is correct, then it means that a normal inhibitory tag of the color word decayed at a faster rate in the schizophrenic subjects than in the controls.

While the present findings are intriguing and demonstrate a dissociation between within-trial and between-trial effects, we cannot rule out the possibility that expectancy effects may have played a role in the failure to find increased within-trial Stroop interference among our subjects (Logan and Zbrodoff, 1979). Nevertheless, the expectancy of the presentation did not create normal negative priming. In addition, in view of our suggestion that the lack of negative priming among the medication-withdrawn schizophrenic patients is a result of decay between trials, it is reasonable to assume that negative priming might vary as a function of the response stimulus interval (RSI). The relationship of RSI and negative priming is an important issue and has been investigated in healthy control subjects (Tipper et al., 1991; Neill and Valdes, 1992; Neill et al., 1992), older adults (Stolzfus et al., 1993), and psychiatric subjects (LaPlante et al., 1992). The findings on the persistence of negative priming are mixed. While some studies have shown that negative priming effects do not decay across RSIs of 2000 ms (Tipper et al., 1991), other studies have found a steady pattern of decay over time (Neill and Valdes, 1992; Neill et al., 1992). It should be noted, however, that even in the experiments that showed a decay, significant negative priming was observed at the long RSIs. This experiment did not control for RSI, but a post hoc analysis examined the RSI for both groups and found no group × RSI interaction ($F = 1.045, df = 1.26, NS$). We recognize that the RSI is an important factor to control for in negative priming research and we are currently carrying out additional experiments in our laboratory to explore the time course of decay in patients with schizophrenia.

The effects of medication also warrant further examination. Since our subjects were withdrawn from medication at the time of testing, it would be important to test a similar group of neuroleptic-treated patients and, if possible, to retest the same patients both on and off medication. Another issue to consider is that the effects that we are observing in these medication-withdrawn patients might be a result of the withdrawal process itself. The patients were withdrawn from their neuroleptic medication for a period of 2 weeks. Clow et al. (1980) noted that 2 weeks after neuroleptic discontinuation the dissociation constant for spiperone reverts to normal, but some behavioral effects take longer to disappear. Since other studies have reported an effect of neuroleptics on cognitive processing (Braff and Saccuzzo, 1982; Braff and Huey, 1988; Nestor et al., 1991), this issue deserves further examination.

Given the complexity of attentional selection in normal subjects and the interaction between semantic and perceptual processing involved in the Stroop task, it is also critical to examine attentional selection in schizophrenic subjects using less complex stimuli in order to dissociate semantic and perceptual effects.

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