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The Effects of Antipsychotic Medication on Sequential Inhibitory Processes

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The authors used a Stroop negative priming paradigm to examine the effects of antipsychotic medication on selective attentional processes. The performance of 14 patients with schizophrenia who were withdrawn from neuroleptic medication was compared with that of 10 medicated patients and 16 matched controls. Results demonstrated an increase in negative priming to normal levels with neuroleptic therapy. In contrast, within-trial interference and facilitation effects appeared to be less sensitive to medication therapy. The sustained inhibition of inhibitory processes over time may differentiate the inhibitory mechanisms of the medication-withdrawn patients from both the medicated patients and the matched controls. The study of sequential inhibitory processes and their response to neuroleptic treatment could be important methods for understanding the temporal parameters associated with inhibition in schizophrenia.

As antipsychotic therapy has become standard in the treatment of schizophrenia, the effects of neuroleptic medication on cognition have been of keen interest to researchers of schizophrenia (see King, 1990; Spohn & Strauss, 1989 for reviews). Deficits in the ability to inhibit irrelevant information have long been associated with the schizophrenia syndrome (Bleuler, 1911; Knaepelin, 1919), and it has become critical in recent years to determine which deficits are an integral component of the disease process and which deficits are a consequence secondary to the medication therapy itself (see King, 1990; Spohn & Strauss, 1989 for reviews).

A number of cognitive tasks have been used to measure the effect of antipsychotics on cognitive performance in patients with schizophrenia. Although some research has failed to find an effect of neuroleptics on cognitive functioning, others have reported an improvement in sustained attentional processes with the introduction of antipsychotic medication (Corbitt & Keilp, 1993; King, 1990; Nestor et al., 1991).

Deficits in selective attention among schizophrenic patients have been linked with the inability to inhibit irrelevant information (Bleuler, 1911). If in the process of selection one must inhibit distracting information, what is the fate of that irrelevant information on subsequent selection? Tipper (1985) proposed that when previously ignored information subsequently becomes the target to be selected, the response of participants is slowed because of the previous inhibition of that information. Tipper called this phenomenon 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 \( n \)). According to Tipper's model, participants who are deficient on within-trial inhibition should show a lack of negative priming across trials. If Tipper's model of negative priming is correct, it could provide a strong theoreti-

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stration of certain medications can alter performance on tasks that require the sustained attention across trials. Beech et al. showed that acute doses of chlorpromazine (a dopamine antagonist) increased the level of negative priming in "normal" controls. This finding suggests that antipsychotics which block dopamine, may alter performance on tasks that involve the sustained attention of information across trials and could create increased negative priming effects in schizophrenic patients. Previous research has reported a lack of negative priming in schizophrenic patients when presenting antipsychotic medication (Beech, Powell, McWilliam, & Claridge, 1989; Laplante, Everett, & Thomas, 1992) and in medication-withdrawn schizophrenic patients (Salo, Roberton, & Nordahl, 1996). If negative priming reflects the sustainment of an inhibitory tag across trials, it is reasonable to hypothesize that an improved sustained attention processing may correlate with an increase in negative priming.

In the present study, we used a computerized single-trial version of a negative priming task using Stroop stimuli to measure the effects of antipsychotic treatment on sequential inhibitory processes in schizophrenic patients. The use of Stroop stimuli (Stroop, 1935) in a negative priming paradigm allows for the examination of both within-trial interference and facilitation and between-trial inhibitory processes. Dalrymple-Alford and Budyk (1966) were the first to use Stroop stimuli in a negative priming procedure to examine inhibition in young normal participants. They found that when lists of Stroop words were presented to participants, the structure of the lists contributed to increased reaction times in word naming. Reaction times were longer on lists where the ink color to be named was preceded by the corresponding color name, compared with lists in which adjacent Stroop words were unrelated. Thus reaction time to name the ink color of the word blue written in red ink was slower when it was preceded by the word ink written in green ink than when it was preceded by yellow written in green ink. Using the same Stroop stimuli and procedure as in our previous study (Salo et al., 1996), we retested as many as possible of our original sample of medication-withdrawn schizophrenic patients after they were stabilized on antipsychotic medications. We also included a group of new patients who were currently receiving antipsychotic drug therapy.

Method

Participants

We tested 24 schizophrenic outpatients and 16 matched controls at the University of California Medical Center in Sacramento. Twelve of the patients were volunteers in an investigational drug study, and 12 were outpatients at the clinic who were not part of the pharmaceutical study. The patients in the investigational drug study were typically seeking an antipsychotic medication with fewer side effects than their current medication. All patients met diagnostic criteria for chronic schizophrenia according to the third revised Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; American Psychiatric Association, 1987). We screened patients and controls using a semistructured psychiatric interview based on the Structured Clinical Interview for the DSM-III-R (SCID; Spitzer & Williams, 1986), both upon entry into the study and on the day of cognitive testing (information available on request). All patients tested in the off-medication (off-meds) condition had been withdrawn from antipsychotic medication for at least 2 weeks prior to testing in a discontinuation design (see Spohn & Strauss, 1989 for a review). None of the patients were neuropsychologically naive. In addition, no anticholinergic medications or short acting benzodiazepines had been taken 48 h prior to the study. All patients had been screened for head injury and none had reported substance abuse within the previous 12 months. Twelve of the medication-withdrawn patients had been participants in our previous study (Salo et al., 1996) and 2 were new to this study. Seven of the 24 patients were tested twice (once on and once off meds) using a counterbalanced crossover design (Spohn & Strauss, 1989). Thus, these patients served as their own controls with the testing order counterbalanced to avoid practice effects. Nine of the patients were tested off meds only and 8 were tested on-meds only. Thus, we tested 16 patients in a medication-withdrawn state, and we tested 15 on medication. Of the entire group of patients, we classified 21 as a paranoid subtype, and we classified the remaining 3 of a undifferentiated subtype.

We tested 16 control participants. The control participants' data have been previously reported in our earlier study (Salo et al., 1996). We matched the 16 controls to the schizophrenic participants on age and years of parental education. To match approximately for socioeconomic status, chronicity of illness and mean age of illness onset did not differ statistically between the two groups of schizophrenic patients: chronicity, \( r(22) = .154, p > .05\), and age of onset, \( r(22) = .162, p > .05\). All participants were right handed and had no history of head injury. In addition, they reported no history of substance abuse within the last 12 months. All participants reported normal color vision. The schizophrenic group included 17 mm and 7 women, whereas the control group was composed of 9 men and 7 women. We paid both patients and controls for their participation in the study and all gave informed consent.

Apparatus

The experiment was programmed on an IBM-compatible computer using the Micro Experimental Laboratory (MEL) version 2.0. Testing took place in a quiet, dimly lit room. We presented Stroop stimuli on an Everex color monitor with the presentation of the stimuli controlled by an Everex 386SX microcomputer (Everex Corp., Fremont, CA). Response timing was to 1-ms resolution and was controlled by a 8253 chip. Stimulus timing was tied to the vertical sync pulse. We recorded all reaction times using a Gerbrands (Gerbrands Corp., Arlington, MA) voice-operated relay interface with the computer and monitored through the gamesport.

Stimuli

We presented stimuli in one of four colors: red, blue, yellow, or green, and we displayed them using 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 color ink. Within-trial neutral stimuli consisted of 50% animal names (Tiger, Bear, Monkey, Dog) printed in one of the four colors of ink and 50% strings of X's printed in one of the four colors of ink. Seventy percent of the trials were incongruent, 15% were neutral, and 15% were congruent. We calculated within-trial Stroop interference by subtracting the mean reaction time on neutral trials from the mean reaction time on incongruent trials. We calculated within-trial Stroop facilitation by subtracting the mean reaction time on congruent trials from the mean reaction time on neutral trials.

We evaluated sequential relations using Stroop stimuli by subtracting 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 an unrelated pair. Unrelated pairs are pairs of trials in which there was no overlap of color on either word or ink (e.g., RED printed in blue ink followed by GREEN printed in yellow...
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ink). The first trial (trial \( n - 1 \)) was not analyzed for negative priming
costs, thus it served as a filler and was always an incongruent trial.
Within each block, 25% of the trials were related, 25% were unrelated,
and 50% were fillers. We presented a total of 400 trials—6 experimental
blocks (each containing 60 trials) and 2 practice blocks (each containing
20 trials). We did not include the practice blocks in the analysis.

Procedure
We instructed participants to say aloud (as rapidly as possible) the
color of ink that the words were printed in while ignoring the word
itself, and we gave instructions that discouraged a speed–accuracy trade
off. The experiment was run on a computer with a black screen followed by the stimulus at
the center of the screen. The onset of the participants’ voice triggered
the voice-operated relay switch (recorded by the composer to the nearest
ms) and terminated the stimulus display on the screen. The experimenter
then typed in the first letter of the participant’s response, which recorded accuracy.
The experimenter’s response initiated the subsequent trial and recorded the response stimulus interval between trials. After 20 practice
trials, we presented participants with 3 blocks of 60 trials each. After
the first 3 experimental blocks, we gave a 2-minute break followed by a
second practice block and the final 3 experimental blocks. All experi-
mental blocks were counterbalanced for order using a Latin square
design.

Data Analysis
We computed mean reaction times for correct responses for each
participant after trimming responses that were more than 3 standard
deviations from the overall mean for each participant, or faster than 150
ms. No more than 5% of the trials were eliminated for any patient (range
= 0–19) or control participant (range = 0–18).

We used analysis of variance (ANOVA) procedures for mixed design
to analyze the data in two separate analyses. We chose this design over a
single ANOVA because the experimental design did not include a
neutral condition on trials used to calculate negative priming, thus mak-
ing it impossible to look at the relationship between Stroop interference
and negative priming with a single analysis.

In analyzing the data for group effects, we included only the first
testing session for all participants, thus avoiding any confounds of prac-
tice effects. The first analysis evaluated negative priming effects with group
(off meds vs. on meds vs. control) as a between-subjects variable
and word type (unrelated vs. related) as a within-subjects variable.
The second analysis evaluated within-trial Stroop effects with group
(off meds vs. on meds vs. control) as a between-subjects variable and
word type (congruent, neutral, incongruent) as a within-subjects variable.

Results

Analysis 1: Between-Trial Effects (Negative Priming)

Group effects. Table 1 displays the mean reaction time for each
between-trial word type condition. There was a main effect of
group, \( F(2, 37) = 4.85, p < .02 \). Planned comparisons
showed that schizophrenic groups both on and off meds had
significantly longer response times than controls: unmedicated vs.
controls, \( F(1, 28) = 8.72, p < .01 \); medicated vs. controls,
\( F(1, 24) = 9.17, p < .01 \). The two schizophrenic groups did not
differ from each other \( (F < 1) \). The main effect of wordtype
pair was not significant, \( F(1, 37) = 2.95, p = .09 \), but more
important, there was a significant interaction between word type
and group, \( F(2, 37) = 3.83, p < .05 \). There was a 39-ms
negative priming effect for the control participants that was
similar in magnitude to that of healthy normal participants re-
ported in the literature (Neill, 1977) and a 43-ms negative priming
effect for the medicated schizophrenic patients. Medicated
schizophrenic patients and controls showed comparable negative priming
effects, whereas the medication withdrawn patients ex-
hibited a lack of negative priming; for on-meds patients versus
controls, \( F < 1 \), for off-meds patients versus controls, \( F(1, 28)
= 5.20, p < .05 \).

Note. meds = medication.

* The increased interference effect of 110 ms is due to 1 participant with a
439-ms interference. When his data were removed from the analysis,
the interference dropped to 79 ms.

Table 1 Mean Reaction Times for Between-Trial and Within-Trial
Word Types Across Groups (in Milliseconds)

<table>
<thead>
<tr>
<th>Wordtype</th>
<th>Off meds (n = 14)</th>
<th>On meds (n = 10)</th>
<th>Controls (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Between-trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>1,033</td>
<td>314</td>
<td>981</td>
</tr>
<tr>
<td>Related</td>
<td>1,010</td>
<td>273</td>
<td>1,024</td>
</tr>
<tr>
<td>Negative priming</td>
<td>23</td>
<td>93.5</td>
<td>-43</td>
</tr>
<tr>
<td>Within-trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congruent</td>
<td>857</td>
<td>125</td>
<td>891</td>
</tr>
<tr>
<td>Incongruent</td>
<td>985</td>
<td>213</td>
<td>1,015</td>
</tr>
<tr>
<td>Neutral</td>
<td>905</td>
<td>250</td>
<td>905</td>
</tr>
<tr>
<td>Interference</td>
<td>80</td>
<td>69</td>
<td>110</td>
</tr>
<tr>
<td>Facilitation</td>
<td>48</td>
<td>87</td>
<td>14</td>
</tr>
<tr>
<td>Error data</td>
<td>.10</td>
<td>.17</td>
<td>.08</td>
</tr>
</tbody>
</table>

Negative priming and repeated measures analysis. Because
seven patients were available for testing both on and off medica-
tion, we could also evaluate the participants with medication
status as a within-subjects variable. Planned comparisons re-
vealed a significant difference between the two conditions (on
vs. off meds), \( t(6) = 2.34, p = .05 \). We tested 5 of the particip-
ants off meds in the first testing session, and we tested 2 of
the participants on meds in the first session. Although the 7
patients exhibited significant negative priming when tested on
medication (61 ms), they failed to exhibit negative priming
when withdrawn from medication and in some cases were faster
on the related pairs. All 7 patients showed an increase in negative
priming in the medicated state regardless of the order in which
they were tested.

Analysis 2: Within-Trial Effects

Group effects. Table 1 displays the mean reaction time for each
group for each condition. Analyses revealed a main effect of
group, \( F(2, 37) = 7.78, p < .01 \), and word type, \( F(2, 74) = 35.7, p < .001 \), but no interaction between group and word
(type \( F < 1 \)). Although the lack of a significant interaction

1 Analyses revealed no interaction between group, neutral, and word
type \( F < 1 \), thus all reported analyses were carried out collapsed
across both neutral types.
cannot demonstrate that medication status does not affect sequential inhibitory processes, it is consistent with an interpretation that within-trial effects are less sensitive to medication status.

Repeated measures analysis. We analyzed within-trial data for the 7 patients tested both on and off medication with medication status as a within-subjects variable. There was no interaction between medication and within-trial word types (F < 1).

Error Analysis

We analyzed errors in the same design. Mean error rate for each group is reported in Table 1. There was a main effect of group, F(2, 37) = 3.17, p = .05, and word type, F(2, 74) = 46.05, p < .001, as well as an interaction between group and word type, F(4, 74) = 3.47, p < .05. Planned comparisons showed that both groups of schizophrenic patients made significantly more errors than age-matched controls, off meds versus controls, F(1, 28) = 5.42, p < .05, on meds versus controls, F(1, 24) = 8.33, p < .01, but did not differ from each other (F < 1). Post hoc analyses revealed that both schizophrenic groups made more errors on the incongruent word type than controls, off meds versus controls, t(28) = 2.5, p < .05, on meds versus controls, t(24) = 2.6, p < .05, but did not differ from each other on incongruent errors (F < 1). There was no difference in error rate between the patients and the controls on either the neutral, F(2, 37) = 1.98, p > .05, or congruent word types (F < 1). Additional error analyses on the trials used to calculate negative priming revealed no difference between the three groups (F < 1). In addition, there was a positive correlation between reaction times and errors, suggesting that there was no speed-accuracy trade off (r = .27). Participants with faster reaction times made fewer errors than those with longer reaction times.

Discussion

The results demonstrate a change in sequential inhibitory processes as a consequence of medication state. Although the schizophrenic patients who were withdrawn from medication failed to exhibit normal negative priming, the patients who were currently on antipsychotic medication did not differ significantly from matched controls. 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 medication-withdrawn schizophrenic patients may be one piece of evidence that the product of selective attention degrades or dissipates over time. Although both groups of schizophrenic patients exhibited more errors than the control participants on incongruent trials, both medicated and medication-withdrawn patients demonstrated equivalent Stroop interference and facilitation as measured by reaction time. Although increased facilitation has been reported in nonparanoid patients (Carter, Robertson, & Nordahl, 1992), it is not surprising that we failed to find increased facilitation in our predominate paranoid patient group. It is also quite possible that within-trial effects are less sensitive to the effects of antipsychotic medication than negative priming. Patients withdrawn from medication may be capable of inhibiting irrelevant information to the same degree as controls, but it is the sustainment of these inhibitory processes over time that differentiates the inhibitory mechanisms of the medication-withdrawn patients from both the medicated patients and the matched controls. This finding is consistent with a rapidly decaying trace of an inhibitory tag and is also commensurate with other interpretations of negative priming that suggest that negative priming represents an episodic memory trace of inhibitory processes that occurred on a previous trial (Neill, Valdes, Terry, & Gorfein, 1992).

Unlike medicated schizophrenic patients and control groups reported on in earlier studies (Beech et al., 1989; Laplante et al., 1992), the medicated patients and control participants in our study exhibited the same levels of negative priming. One possible reason for the discrepancies in results could be differences in methodology. As in our study, Laplante et al. used Stroop stimuli, but unlike us, they used a manual response with four response options to measure both within-trial interference and between-trial negative priming. Modality of response is known to affect the level of within-trial Stroop interference (see MacLeod, 1991 for a review) and it is possible that use of a manual response could also affect the sustainment of inhibition across trials because of the added load of remembering the stimulus–response mapping. In addition, because antipsychotics block dopamine receptors in the basal ganglia, the interpretation of results from an experimental procedure using a manual response must consider the effects of the medication on basic manual motor coordination.

Although the study by Beech et al. (1989) also used a vocal response to measure response latency, the stimulus duration that was used was very short (100 ms). Stimulus duration has been shown in other research to affect the amount of negative priming exhibited, supporting the hypothesis that negative priming takes time to develop (Allport, Tipper, & Charnel, 1985). It is quite possible that with a brief, masked stimulus presentation (100 ms), the medicated patients who were tested were either unable to fully process the stimulus, such that significant between-trial inhibition would be observed, or the brief stimulus presentation did not allow sufficient time for inhibitory processes to develop (Sacuzzo & Braff, 1981).

Many studies that have examined the effects of neuroleptics on cognitive function are cross-sectional in design (i.e., separate groups of medicated and unmedicated patients; see Spohn & Strauss, 1989, for review). It is always possible, however, that group differences in these studies could be related to factors other than the medication treatment itself. By using a test–retest method in addition to a cross-sectional design, we were able to evaluate medication effects with regard to individual patients. Given the difficulty of implementing drug-withdrawal studies in schizophrenic patients and the challenge of monitoring and retesting the patients over extended time intervals, a combined approach using both cross-sectional and test–retest methods can be informative.

More research is needed to examine the effects of antipsychotic medication on sequential inhibitory processes. The Stroop negative priming task is a powerful tool for examining the time course of inhibition in patients with schizophrenia, as it allows

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1 All post hoc analyses were corrected using the Bonferroni method.
for the measure of both within-trial and between-trial effects with a tightly integrated stimulus. We are proposing that the increase in negative priming with neuroleptic therapy may represent the strengthening of inhibitory memory traces in patients with schizophrenia. Negative priming paradigms provide researchers with very sensitive measures of inhibitory memory traces, ranging from 300 ms to several seconds. Temporal disso-
ciations in the duration of inhibition may provide valuable data about chemical pathways and neural regions involved in schizo-
phrenia. The study of sequential inhibitory processes and their response to neuroleptic treatment may help us to better understand the temporal parameters associated with inhibition in schizophrenia.

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