α2-Noradrenergic effects on ERP and behavioral indices of auditory information processing

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Abstract

Norepinephrine is believed to modulate CNS processing of environmental signals. However, its specific role in stimulus evaluation processes has not been delineated. We examined the effects of the α2 noradrenergic agents, clonidine and yohimbine, on ERP and performance measures of auditory information processing. Ten healthy participants performed a three-tone target detection experiment, receiving either placebo, 0.2 mg clonidine, or 30 mg yohimbine, in a double-blind randomized design. The principal locus of action of the noradrenergic agents occurred between 100 and 200 ms poststimulus. P200 latency was sped by yohimbine and slowed by clonidine, and the frontal P3a was shifted in tandem. Components related to target detection (N250 and P3b) were unaffected. The results suggest that norepinephrine modulates CNS mechanisms of selective attention to infrequent stimuli. This may be relevant for patients with schizophrenia, a subset of whom exhibit selective abnormalities of these same ERP components. Our results offer a possible link between these two sets of findings, suggesting that some patients with schizophrenia may have dysfunctional noradrenergic systems.


An inability to properly attend to environmental stimuli is thought to be an intrinsic part of the phenomenology of schizophrenia and other psychoses (McGhie & Chapman, 1961). Consistent with this, electrophysiologic studies of information processing deficits in schizophrenia have documented abnormalities of both early stimulus filtering, as indexed by the P50 suppression ratio (Adler et al., 1982, 1990; Freedman, Adler, Waldo, Pachman, & Franks, 1983), and subsequent stimulus evaluation, as indexed by the amplitude of the P300 (Braff, 1993; Turetsky, Colbath, & Gur, 1998). An understanding of the neuropharmacologic mechanisms that underlie both normal and abnormal modulation of these electrophysiologic components may therefore help to elucidate the neurobiology of the cognitive and attentional impairments associated with these disorders (Adler et al., 1994). The clinical pathophysiology of psychotic illnesses is thought to involve disturbances of central catecholamine systems, so it is reasonable to suspect that disturbances of these neurotransmitter systems also underlie patients' information processing deficits. However, there is very little evidence linking catecholaminergic activity with the types of information processing deficits exhibited by psychotic patients. Indeed, the weight of the evidence derived from studies of the neuropharmacology of human information processing suggests that drugs that alter the cholinergic system (e.g., scopolamine) affect stimulus evaluation processes, whereas stimulant drugs (e.g., amphetamine, methylphenidate) primarily affect motor responses (Callaway, 1984; Callaway, Halliday, Naylor, & Schechter, 1985).

Nevertheless, there are reasons to suspect that the noradrenergic neurotransmitter system plays a role in the cognitive processes pertinent to stimulus evaluation. Based primarily on animal, rather than human, research, a theoretical model of noradrenergic activity has been proposed wherein norepinephrine modulates the relationship between CNS processing of incoming signals versus the processing of "noise" in the environment. In this model, the noradrenergic system is thought to augment processing of important information while attenuating processing of less relevant stimuli, thereby increasing the effective signal-to-noise ratio (Aston-Jones, Rajkowski, Kubiat, & Alexinsky, 1994; Oades, 1985). One study of human information processing, utilizing agents that specifically affect the α2 noradrenergic system, concluded that the noradrenergic system affects relatively early encoding of visual stimuli (Halliday, Callaway, & Lannon, 1989). Studies of auditory sensory gating mechanisms, both in animals and in patients with schizophrenia and bipolar affective disorder, have also suggested that the noradrenergic system may be involved in the early filtering of sensory stimuli (Adler, Pang, Gerhardt, & Rose, 1988; Baker et al., 1987; Braff and Geyer, 1990). In a relatively direct test of this hypothesis, the α2 antagonist yohimbine was shown to increase the P50 suppression ratio in normal adults, suggesting reduced auditory sensory gating (Adler et al., 1994).

We report here on the effects of the selective α2 noradrenergic agonist clonidine and the α2 antagonist yohimbine on auditory ERP measures related to cognitive stimulus evaluation processes. Acting via a presynaptic negative feedback mechanism, clonidine inhibits norepinephrine turnover and release and decreases MHPG...
Experimental Procedure

Opposite effect of blocking negative feedback following the release of norepinephrine and increasing MHPG (Kehe & Davis, 1985). We hypothesized that these pharmacologic agents would have opposite effects on behavioral and ERP measures associated with the evaluation of task-relevant stimuli, thereby implicating norepinephrine in the modulation of these processes. In particular, we hypothesized that a frontal subcomponent of the P300 (P3a), which is thought to denote the cognitive equivalent of an orienting response to novel stimuli (Knight, 1984; Squires, Squires, & Hillard, 1975), would be affected by these manipulations.

Methods

Participants

Ten male volunteers between the ages of 22 and 37 were recruited from the community. Participants were interviewed and examined by a psychiatrist (B.T.) to ensure that there was no history of previous medical or neuropsychiatric illness, substance abuse, head injury, hearing difficulties, or any other contraindication to the use of noradrenergic agents. None of the participants had a family history of a psychiatric illness and none were being treated with medications at the time of study. All participants gave informed consent prior to participation.

Experimental Procedure

Each participant was tested on three separate occasions spaced at least 1 week apart. At each session, the participant’s threshold for discriminating between a 60-dB SPL 1000-Hz tone and a second tone of higher frequency was determined. An alternating ascending and descending “method of limits” procedure was used, with a forced-choice “same” or “different” response, to identify the threshold defined as that frequency at which a correct discrimination from a 1000-Hz tone was made on 50% of the trials.

This was done in an effort to standardize the difficulty of the subsequent auditory target detection task across participants and sessions. Threshold frequencies ranged from 1004 Hz to 1021 Hz across all participants and sessions, with no within-subject differences across the 3 test days. *F*(2,18) = 0.34, *p* = .72. EEG electrodes were applied and the participant was given a predrug, or baseline, test. One of three possible oral medications was then administered: placebo, 0.2 mg clonidine, or 30 mg yohimbine. The drugs were given in identical vehicles, the order of the drugs was randomized across participants, and both the examiner and the participant were blind to the drug given. A postdrug test was given 75 min after ingestion. Subjective response to each medication was assessed by the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971), which the participant completed before and after both the pretest and the posttest. Blood pressure (BP) and pulse were recorded 5 and 30 min predrug, and 30, 60, 90, and 120 min postdrug.

Task

A three-tone auditory target detection task was employed. A series of 60-dB SPL tones was presented binaurally through headphones. The duration of each tone was 40 ms: the interstimulus interval varied randomly between 1.5 and 1.6 s. Seventy percent of the tones were 1000 Hz “standard” tones; 15% were 950 Hz, designated as a rare “nontarget”; and 15% were higher frequency “target” tones, to which the participant was expected to respond by lifting the right index finger. Tones were presented in two separate blocks and the ordering of target, nontarget, and standard tones was randomized within each block. The actual target frequency was independently set for each participant at each session, based on the discrimination threshold determined that day. In the first block, the difference between the target and the 1000-Hz standard was four times that of the threshold frequency (e.g., if the threshold frequency were 1015 Hz, then the target frequency was 1060 Hz). In the second block, the discrimination of target from standard was more difficult, that is, a standard-target difference two times that of the threshold (e.g., 1030 Hz target). To assess drug effects on task performance, separate records were kept of the number of correctly identified targets (hits), erroneously identified standard and nontarget tones (false responses), and the reaction time for each correctly identified target.

ERP Recordings

Electrodes were applied at Fpz, Fz, Cz, Pz, and Oz. Four additional electrodes were placed along the midline, midway between the following pairs: Fpz and Fz, Fz and Cz, Cz and Pz, and Pz and Oz. This montage provided a chain of nine equidistant electrodes overlaying the mid sagittal plane. All scalp electrodes were referenced to the left ear. A1. The electrooculogram (EOG) was recorded between two electrodes placed above the left outer canthus and below the right outer canthus. EEG and EOG were amplified with a Grass Model 7B polygraph (60 Hz filter, band pass = 0.1–35 c/s). Each channel of EEG was sampled every 4 ms from 40 ms prestimulus to 760 ms poststimulus. The data for any single trial were rejected if the EOG was greater than 35 μV baseline to peak or if there was A/D converter saturation (± 125 μV) on any of the EEG channels.

Stimuli were presented until 32 correctly classified trials without EOG artifact or A/D saturation were recorded for both the rare nontarget and target conditions for each block of tones. The total number of stimulus presentations ranged from 221 to 666 across all participants, sessions, and conditions (mean = 323 = 90.2 SD). This did not vary across the three sessions, independent of the active drug effects discussed below. *F*(2,18) = 1.02, *p* = .38. Average waveforms were computed from the single trials, separately for each condition (target, nontarget, and standard) within each block of pre- and postdrug trials. The mean amplitude of the 40 ms prestimulus interval was subtracted from each waveform to obtain a mean 0 prestimulus baseline.

Data Reduction and Statistical Analysis

To disentangle temporally overlapping ERP components, each set of common-referenced average waveforms was first converted to a set of current source density (CSD) estimates, by applying a linear transformation matrix that approximated the Laplacian source operator (Hjorth, 1975, 1980). Mathematically, this was equivalent to employing a local average reference for each recording site, based on the average of the electrical potentials derived from the two electrodes immediately adjacent to it (anterior and posterior). This yielded CSD data for seven electrodes, excluding the two peripheral sites, Fpz and Oz. CSD recordings minimize the electrical distortions produced by the skull and scalp, and represent reference-independent sources and sinks in the scalp electrical field. CSD measurements represent, almost exclusively, the activity of topographically localized cortical sources. More distal sources do not contribute to the CSD measures at an individual electrode site. This is in marked contrast to common-reference derived voltage potentials. Consequently, the presence of topographically discrete sources in the CSD data must reflect the activity of distinct dipole sources.
Figure 1, depicting spatiotemporal contour plots of the grand average pretest data, demonstrates how the CSD transformation facilitates the spatial separation of temporally overlapping components by providing much finer spatial localization. Note, in particular, that the CSD plots reveal two spatially discrete sources of activity, between 300 and 400 ms, that were not separable in the ear-referenced data: a frontal source present in both rare nontarget and target conditions and a somewhat later parietal-occipital source present only in the target condition. The delineation of these two discrete sources is consistent with previous suggestions that the scalp P300 is comprised of at least two temporally overlapping, but spatially and functionally distinct subcomponents: P3a, which occurs slightly earlier, has a frontocentral topographic scalp distribution, and reflects attentional orienting to novel or infrequent stimuli, and P3b, which has a parietal scalp maximum and reflects cognitive processes associated with target identification (Squires et al., 1975). As will be shown below, when the latencies and amplitudes of these two overlapping sources are disentangled via CSD transformation, their patterns of response to experimental effects are different, validating the idea that they are neuroanatomically and functionally distinct subcomponents of the P300.

Based on the grand average plots, a focal scalp electrode and temporal window were selected for the CSD activity of each of five ERP components: N100, P200, N250, and the separate frontal (P3a) and parietal (P3b) subcomponents of the auditory P300 (Table 1). The latency of each component was then defined as the point of peak activity, within the specified time window, at the electrode of interest. Component magnitude was defined as the integrated amplitude within a 48-ms window, centered around the peak latency.

Summary measures of task performance, which were computed for each block of trials, included the mean reaction time for correctly identified target tones, the percentage of targets that were correctly identified (hit rate), and the percentage of standard tones that were falsely identified as targets (false response rate). Rare nontarget tones were not included in the measurement of false alarms because there were essentially no misclassifications of these lower frequency tones. Additionally, in a signal detection
analysis, we computed independent measures of participants' ability to discriminate between targets and standards (d') and their response bias or criterion for responding affirmatively when uncertain (Cj) (Corwin, Peslow, Feenan, Rotrosen, & Fieve, 1990; Snodgrass & Corwin, 1988). Responses to the POMS were scored to yield measures for each of the six POMS subscales (tension, depression, anger, vigor, fatigue, and confusion).

Each dependent variable was examined using a repeated measures multivariate analysis of variance design. For each ERP measure, there were four within-subject factors: (a) drug type (placebo vs. clonidine vs. yohimbine); (b) pretest versus posttest; (c) task difficulty (easy vs. hard discrimination); and (d) condition (target vs. rare nontarget). For the various performance measures, there were three factors (condition effect and similar), for the POMS, there were three factors (drug type, pre/post, subscale). For BP and pulse, there were two factors (drug type and time). In all cases, effects of the pharmacologic probes could be observed as significant Drug × Pre–Post interactions. Null hypotheses were rejected for values of p < .05, two-tailed.

Results

Hemodynamic Changes
Clonidine and yohimbine had opposite effects on participants' cardiovascular systems. Statistically significant Drug × Time interactions were observed for both systolic, F(8,72) = 15.73, p < .0001, and diastolic, F(8,72) = 8.51, p < .0001, blood pressure. In individual contrasts, clonidine lowered systolic BP relative to baseline at 60 (−10.7 mmHg), 90 (−19.1 mmHg), and 120 (−17.9 mmHg) min postdrug ingestion. Yohimbine, in contrast, raised systolic BP at 60 (5.3 mmHg) and 120 (+6.4 mmHg) min postdrug. Diastolic BP was also reduced by clonidine at 60 (−6.7 mmHg), 90 (−11.5 mmHg), and 120 (−11.2 mmHg) min postdrug, but was not affected by yohimbine. Neither active agent significantly altered pulse rate.

Mood State Measures
There were differential effects of the medications on the various POMS subscales, as indicated by a significant Drug × Pre–Post × Subscale interaction across the three drug types, F(10,90) = 6.67, p < .0001 (Figure 2). Univariate tests revealed significant effects for four of the six POMS subscales: tension, F(2,18) = 8.17, p < .01; vigor, F(2,18) = 5.81, p = .01; depression, F(2,18) = 7.17, p < .01; and confusion, F(2,18) = 4.28, p < .05. Separate paired contrasts between each active drug and placebo revealed significant increases on both the fatigue, F(1,9) = 11.25, p < .01, and confusion, F(1,9) = 6.74, p < .05, subscales after clonidine, and an associated decline in the vigor index, F(1,9) = 12.34, p < .01.

Yohimbine significantly increased subjects' ratings on the tension subscale, F(1,9) = 14.44, p < .01. The increase in confusion postyohimbine was smaller than the increase seen after clonidine and, when compared to placebo, did not reach the significance criterion, F(1,9) = 3.61, p = .09.

Task Performance Measures
Reaction time (RT) was strongly affected by task difficulty. Mean RT increased by 55 ms, overall, when the target was more difficult to detect, 518 ms versus 463 ms, F(1,9) = 44.10, p < .0001. Contrary to our expectations, though, medication did not significantly alter RT. Based on previous work (Halliday et al., 1989), we had expected clonidine to slow and yohimbine to speed, reaction time. Although mean RT did increase by 19 ms after clonidine, compared to a 6-ms decrease after placebo and a 3-ms decrease following yohimbine, this difference was not statistically significant, F(2,18) = 1.06, p = .37.

In contrast to reaction time, measures related to the accuracy of performance did change in response to medication, F(2,18) = 11.63, p < .001. Clonidine significantly decreased the hit rate for correctly identified targets. Hit rate was also reduced when the target was more difficult to discern, F(1,9) = 42.28, p < .0001. However, there was no interaction between the two and no effect of either medication or task difficulty on the false response rate. Signal detection analysis confirmed that the decrease in target hit rate following clonidine resulted primarily from a change in participants' abilities to discriminate the target tone from the standard, rather than a change in response bias, d'; F(2,18) = 11.84, p < .001; C3; F(2,18) = 2.93, p = .07. However, covarying for changes in vigor and fatigue eliminated this clonidine-induced performance decrement. In contrast, covarying for changes in tension revealed a near-significant improvement in performance following yohimbine, F(1,8) = 4.37, p = .06.

Given the decreased hit rate with clonidine, it is not surprising that we also observed an increase in the total number of stimulus presentations required to acquire 32 correctly identified artifact-free target trials, F(2,18) = 12.7, p < .001. Mean number of tones (standards + targets + novels), averaged across easy and hard conditions, was 302.4 following placebo, 418.3 following clonidine, and 292.1 following yohimbine. This difference remained.

Table 1. Electrode Locations and Latency Intervals of ERP Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Electrode</th>
<th>Temporal Window (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N100</td>
<td>Cz</td>
<td>60–120</td>
</tr>
<tr>
<td>P200</td>
<td>Cz</td>
<td>124–228</td>
</tr>
<tr>
<td>N250</td>
<td>Fz/Cz</td>
<td>212–296</td>
</tr>
<tr>
<td>O1</td>
<td>Fz</td>
<td>300–380</td>
</tr>
<tr>
<td>O2</td>
<td>Pz</td>
<td>320–440</td>
</tr>
</tbody>
</table>

1Electrode located midway between Fz and Cz.
marginally significant even after covarying for the effects of sedation. $F(1,8) = 4.91, p = .05$.

**ERP Measures**

Grand average common reference waveforms, pre and post each drug condition, are presented in Figure 3. The means and standard deviations of the CSD amplitude and latency measures derived from these raw waveforms are presented in Table 2. Proceeding from earliest to latest component activity, we observed the following experimental effects.

**N100.** N100 latency and amplitude were both unaffected by the pharmacologic manipulation or by changes in any of the experimental task variables.

**P200.** P200 amplitude did not exhibit any task or drug effects. P200 latency, however, showed a response to medication that was small in magnitude, but statistically highly significant, $F(2.18) = 11.01, p < .001$. In separate paired contrasts, both clonidine and yohimbine altered P200 latency relative to placebo: clonidine delayed the point of peak activity, mean latency delay = 6.4 ms, $F(1.9) = 5.72, p < .05$, whereas yohimbine accelerated its occurrence, mean speeding = 4.6 ms, $F(1.9) = 14.60, p < .01$, compared to placebo (Figure 4). Task difficulty and condition had no effect on the timing of the P200.

**N250.** In contrast to the earlier N100 and P200 components, whose amplitudes were unchanged across the tone conditions, the amplitude of the N250 was strongly affected by condition. N250 was larger for the target than the rare nontarget. $F(1.9) = 10.66, p < .01$, consistent with the idea that this component denotes cognitive processes associated with discriminative stimulus evaluation (Grillon, Courchesne, Ameli, Geyer, & Braff, 1990). N250 amplitude was also altered significantly by medication, becoming more negative following clonidine and less negative following yohimbine. $F(2.18) = 4.74, p < .05$ (Figure 4). This drug effect interacted with task difficulty, $F(2.18) = 3.51, p = .05$. Clonidine affected N250 amplitude when the task was relatively easy: yohimbine affected it when the task was more difficult. Latency was unaffected by medication or condition, but slowed slightly (mean delay = 7 ms) with increasing task difficulty, $F(1.9) = 13.85, p < .01$.

**Figure 3.** Common reference waveforms pre and post each drug condition. Waveforms are grand averages across all participants, both levels of task difficulty and both rare tone conditions. Top row: Fz; middle row: Cz; bottom row: Pz electrode. Left column: placebo; middle column: clonidine; right column: yohimbine.
Table 2. Current Source Density Amplitudes and Latencies: Mean (SD)

<table>
<thead>
<tr>
<th>Target</th>
<th>Placebo</th>
<th>Clonidine</th>
<th>Yohimbine</th>
<th>Placebo</th>
<th>Clonidine</th>
<th>Yohimbine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (μV/cm²)</td>
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<tr>
<td>N100</td>
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<tr>
<td>Predrug</td>
<td>-1.22 (0.51)</td>
<td>-1.55 (1.46)</td>
<td>-0.97 (0.50)</td>
<td>-1.11 (0.41)</td>
<td>-1.24 (1.02)</td>
<td>-0.89 (0.85)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>-0.99 (0.39)</td>
<td>-0.95 (0.73)</td>
<td>-1.04 (0.47)</td>
<td>-1.31 (0.70)</td>
<td>-0.92 (1.19)</td>
<td>-0.96 (0.85)</td>
</tr>
<tr>
<td>P200</td>
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<tr>
<td>Predrug</td>
<td>2.14 (1.40)</td>
<td>1.68 (1.18)</td>
<td>2.38 (1.42)</td>
<td>2.29 (1.42)</td>
<td>1.89 (0.73)</td>
<td>2.36 (1.10)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>2.34 (1.42)</td>
<td>1.79 (1.06)</td>
<td>1.98 (1.21)</td>
<td>2.28 (1.14)</td>
<td>1.78 (0.72)</td>
<td>2.13 (1.22)</td>
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<tr>
<td>N250</td>
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<tr>
<td>Predrug</td>
<td>-1.55 (0.89)</td>
<td>-0.75 (0.80)</td>
<td>-1.47 (0.62)</td>
<td>-0.65 (0.37)</td>
<td>-0.46 (0.36)</td>
<td>-0.65 (0.35)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>-1.56 (0.66)</td>
<td>-1.33 (0.89)</td>
<td>-1.23 (0.87)</td>
<td>-0.40 (0.49)</td>
<td>-0.60 (0.61)</td>
<td>-0.49 (0.42)</td>
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<tr>
<td>P3a*</td>
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<tr>
<td>Predrug</td>
<td>0.79 (0.85)</td>
<td>0.60 (0.46)</td>
<td>0.66 (0.63)</td>
<td>0.77 (0.38)</td>
<td>0.82 (0.34)</td>
<td>0.56 (0.63)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>0.68 (0.37)</td>
<td>0.50 (0.42)</td>
<td>0.84 (0.59)</td>
<td>0.62 (0.55)</td>
<td>0.40 (0.22)</td>
<td>0.66 (0.40)</td>
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<tr>
<td>P3b</td>
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<tr>
<td>Predrug</td>
<td>0.67 (0.55)</td>
<td>0.88 (0.64)</td>
<td>0.87 (0.30)</td>
<td>0.37 (0.40)</td>
<td>0.02 (0.96)</td>
<td>0.42 (0.48)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>0.28 (1.14)</td>
<td>0.49 (0.39)</td>
<td>0.77 (0.60)</td>
<td>0.86 (2.03)</td>
<td>0.19 (0.33)</td>
<td>0.54 (0.35)</td>
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<tr>
<td>Latency (ms)</td>
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<tr>
<td>N100</td>
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</tr>
<tr>
<td>Predrug</td>
<td>97.2 (13.0)</td>
<td>106.4 (13.9)</td>
<td>98.2 (11.4)</td>
<td>95.6 (11.0)</td>
<td>107.2 (13.2)</td>
<td>101.2 (12.9)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>100.8 (14.7)</td>
<td>105.4 (8.7)</td>
<td>99.0 (11.7)</td>
<td>95.2 (10.9)</td>
<td>103.8 (16.2)</td>
<td>98.8 (11.3)</td>
</tr>
<tr>
<td>P200*</td>
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<tr>
<td>Predrug</td>
<td>172.0 (6.4)</td>
<td>179.0 (11.2)</td>
<td>170.4 (5.6)</td>
<td>170.6 (10.1)</td>
<td>172.2 (7.8)</td>
<td>170.6 (10.8)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>171.8 (6.1)</td>
<td>181.2 (14.0)</td>
<td>163.8 (9.4)</td>
<td>171.2 (8.9)</td>
<td>183.2 (13.7)</td>
<td>168.4 (6.8)</td>
</tr>
<tr>
<td>N250</td>
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<tr>
<td>Predrug</td>
<td>249.0 (15.2)</td>
<td>254.4 (25.1)</td>
<td>243.0 (17.2)</td>
<td>246.2 (17.0)</td>
<td>243.2 (20.0)</td>
<td>233.6 (20.9)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>243.8 (15.0)</td>
<td>245.8 (19.5)</td>
<td>247.6 (17.3)</td>
<td>241.8 (19.9)</td>
<td>254.6 (25.4)</td>
<td>244.6 (22.8)</td>
</tr>
<tr>
<td>P3a*</td>
<td></td>
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</tr>
<tr>
<td>Predrug</td>
<td>349.4 (12.5)</td>
<td>359.8 (23.4)</td>
<td>360.0 (15.6)</td>
<td>345.0 (14.7)</td>
<td>348.6 (14.9)</td>
<td>345.8 (16.7)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>354.0 (21.1)</td>
<td>364.0 (22.6)</td>
<td>348.2 (25.5)</td>
<td>342.0 (17.3)</td>
<td>367.2 (12.9)</td>
<td>339.0 (20.6)</td>
</tr>
<tr>
<td>P3b</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Predrug</td>
<td>391.4 (32.4)</td>
<td>393.8 (21.7)</td>
<td>388.6 (22.7)</td>
<td>360.8 (34.5)</td>
<td>356.8 (31.1)</td>
<td>376.6 (33.7)</td>
</tr>
<tr>
<td>Postdrug</td>
<td>384.8 (31.9)</td>
<td>400.6 (25.3)</td>
<td>371.0 (23.2)</td>
<td>364.4 (19.8)</td>
<td>366.4 (23.9)</td>
<td>376.2 (36.6)</td>
</tr>
</tbody>
</table>

Note: Drug × Pre-Post interaction: *p < .05; **p < .01.

P3a. P3a amplitude was significantly altered by the pharmacologic manipulations, \( F(2,18) = 4.34, \ p < .05 \), being reduced by clonidine and increased by yohimbine, relative to placebo (Figure 4). In other words, yohimbine enhanced and clonidine attenuated the cognitive orienting response during the performance of this difficult discrimination task. There were no observable effects of either condition or task difficulty on P3a amplitude.

P3a latency also showed a significant Drug × Pre-Post interaction, \( F(2,18) = 6.13, \ p < .01 \). Overall, clonidine delayed, whereas yohimbine sped, the peak of P3a latency. There were no main effects of task or condition, but a significant Task × Condition interaction, \( F(1,9) = 6.35, \ p < .05 \), reflected selective slowing of the target P3a during the easier task. To determine whether the effect of medication on P3a latency was independent of the effect observed for the earlier P200 (or whether, alternatively, P3a latency was prolonged by clonidine simply because it followed the already delayed P200), we examined the P200 − P3a latency difference. The duration of this interval did not change following medication [Drug × Pre-Post interaction, \( F(2,18) = 0.90, \ p = .42 \)], suggesting that there was no additional effect on P3a latency subsequent to the P200. This is in contrast to the Task × Condition interaction, which persisted when the analysis was restricted to the P2−P3a interval, \( F(1,9) = 7.40, \ p < .05 \).

P3b. The only main effect on the amplitude of the parietal P3b subcomponent was a powerful condition effect, \( F(1,9) = 20.38, \ p = .001 \). As is generally seen for the composite common-reference scalp P300, which exhibits a parietal maximum, the
target amplitude of this subcomponent greatly exceeded that of the rare nontarget. There was a similar effect of condition on P3b latency, \( F(1,9) = 13.73, p < .01 \), with target latency exceeding that of the rare nontarget. However, none of the other experimental variables had a significant effect on this parietal subcomponent. Specifically, there was no effect of medication on P3b amplitude, \( F(2,18) = 0.303, p = .74 \), or latency, \( F(2,18) = 0.85, p = .44 \).

### Relationship of ERP Measures to Mood State and Performance

We considered the question of whether the significant effects of medication on component amplitudes and latencies were correlated, across subjects, with any of the significant affective and behavioral effects of these medications. We computed relative change scores for each of the two active drugs (i.e., post-pre drug difference minus post-pre placebo difference), for each ERP parameter and the various performance and mood state measures that exhibited drug effects. We then examined the intercorrelations among these difference scores across the 10 subjects. Not surprisingly, different mood state measures were strongly correlated with each other. Subjects who experienced a greater increase in tension after taking yohimbine also experienced an increase in confusion \((r = .82, p = .004)\). Similarly, increased fatigue with clonidine was highly correlated with the sense of increased confusion \((r = .78, p = .008)\). There were no significant correlations between changes in mood state and changes in performance produced by the active drugs. In particular, there was no significant relationship between the increased fatigue postclonidine and the decrease in target hit rate \((r = .44, p = .21)\). There were, however, near-significant correlations between increased tension and decreased hit rate \((r = .60, p = .068\), and between decreased fatigue and increased hit rate \((r = .62, p = .054)\) following yohimbine. There was also an association between clonidine’s effect on performance and its effect on P3a amplitude. Subjects who exhibited the greatest P3a amplitude reductions following clonidine ingestion also had the greatest decrements in hit rate \((r = .76, p = .001)\) and discrimination ability \((d’; r = .77, p = .01; \text{Figure } 6)\).

### Discussion

In this study, \( \alpha \)-noradrenergic agents affected mood, performance and ERP measures of CNS activity. The specific alterations in mood state—an increase in tension with yohimbine and a decrease in arousal with clonidine—are consistent with what we might expect to see with changes in norepinephrine levels. The anxiogenic effects of yohimbine, in particular, have been shown to be correlated with changes in levels of the norepinephrine metabolite, MHPG, in individuals prone to panic attacks (Gurguis & Udde, 1990). The fact that both active drugs produced a subjective sense of confusion is also consistent with the inverted U-shaped relationship that exists between arousal and efficiency of performance (Eysenck, 1982). That is, performance capacity tends to be impaired by activation that is either too low or too high relative to some optimum level. The consistency of these mood effects, coupled with the expected effects on systolic BP, provides confidence that the medications acted as intended and that the other behavioral and ERP changes that we observed may, in fact, be attributed to manipulations of the noradrenergic system.

With respect to behavior, clonidine’s effect on hit rate and discrimination ability \((d’)\) paralleled the changes seen with an actual increase in task difficulty and could, therefore, be interpreted as a reduction in the effective signal-to-noise ratio associated with a decrease in noradrenergic tone. Alternatively, the decrease in target detection rate might simply be a nonspecific by-product of the increased sedation associated with clonidine. To link these performance changes unambiguously to changes in noradrenergic activity level, we would hope to see opposing effects for clonidine and yohimbine, which we did not find.

Yohimbine’s failure to enhance target discrimination may simply reflect the fact that the power of this study, with its relatively small sample size, is low. However, given that a number of other drug effects were observed, it also raises questions about the hypothesized signal versus noise “tuning” function of norepinephrine. If norepinephrine facilitates the selective processing of relevant stimuli, then we might expect to see an improvement in target detection, particularly in the more difficult task. In fact, though not statistically significant, performance on this task did improve somewhat following yohimbine \((80\% \text{ correct predrug, } 86\% \text{ correct postdrug})\), whereas it remained constant with placebo \((76\% \text{ predrug, } 77\% \text{ postdrug})\), and was markedly worse following clonidine \((77\% \text{ predrug, } 58\% \text{ postdrug})\). The absence of a more robust association between yohimbine and target sensitivity might reflect, in part, a ceiling effect. For a group of normal subjects with intact noradrenergic systems who are engaged in a difficult task very little additional upward tuning of the cognitive processing appa-
ratios may be possible. The results might be different in individuals whose noradrenergic systems are not functioning at an optimum level (e.g., clinical populations such as patients with depression or schizophrenia).

Another possibility is that the specific dose of yohimbine was not optimal for enhancing task performance. Consistent with the inverted-U relationship between arousal and performance, we would expect performance enhancement only within a limited dosage range, which might vary from person to person. The fact that yohimbine produced a sense of tension and that performance changes approached significance when we covaried for this mood state suggests that, for some of our subjects at least, the dosage may have been too high. It is noteworthy, in this regard, that 6 participants showed mild performance deficits following yohimbine, whereas 4 showed more marked performance enhancements. The correlation between performance decrement and tension increase was \( r = .06 \). Participants with performance decrements may have, in effect, overshoot the peak of the inverted-U and landed instead on its downward slope.

A third issue that must be considered is timing of the ERP and performance measures relative to the time of drug ingestion. We chose to begin testing subjects 75 min after drug ingestion, with the test period lasting \(-20\) min. To maintain the double-blind design of the study, the postdrug delay was required for clonidine and yohimbine. Adler, however, in his study of the effects of yohimbine on P50 auditory sensory gating (Adler et al., 1982), used a 15-min delay, based on evidence that peak effects on the acoustic startle response and panic induction both occur within 30 min of drug ingestion. Coincident with peak plasma catecholamine changes. It is possible, therefore, that the effects of yohimbine were attenuated simply because we waited too long to assess them. However, plasma MHPG levels remain elevated for up to 4 hr postingestion of yohimbine (Charney et al., 1984; Krystal et al., 1992) and there are several reports of CNS effects of yohimbine, using both comparable dosages and delays exceeding 75 min. These include observations of enhanced memory (O’Carroll, Drysdale, Cahill, Shajahan, & Ehrmeier, 1999), augmented acoustic startle response (Morgan et al., 1993), increased “nervousness” (Charney et al., 1984), and decreased reaction time (Halliday et al., 1989). Also, as noted above, the correlation between increased tension and decreased accuracy is most readily interpretable as an excessive, rather than attenuated, yohimbine response. So, although the time delay may be of some importance, we do not consider it to be a primary factor in understanding these findings.

The electrophysiologic data permit us to more precisely delineate those cognitive subprocesses that are affected by noradrenergic modulation. Clonidine and yohimbine had significant opposing effects on the latencies of P200 and P3a, with yohimbine speeding and clonidine slowing peak latency. In contrast, there were no effects on the latencies of the intervening N250 or the overlapping P3b. These chronometric data can be understood using a serial versus parallel processing model of the timing stimulus evaluation mechanisms (Callaway, 1984; Callaway et al., 1985; Frowein, Gaillard, & Varey, 1981; Halliday, Callaway, Naylor, Grazinger, & Prael, 1986; Halliday et al., 1989). According to this model, (a) when a pharmacologic agent has an equal effect on the latencies of two components that occur in sequence (e.g., P200 and P3a), the processes represented by these two measures are thought to be serially yoked to each other and the action of the pharmacologic agent can be localized to the interval prior to the earlier measure; (b) when a drug affects the latency of a later component, but not an earlier measure (e.g., P200 and N100), then the effect of the agent can be localized to the interval between the two; (c) when a drug affects the latency of an early component but not a later one (e.g., P200 and N250 or P3b), then the processes represented by these two measures are thought to occur in parallel, with the pharmacologic effects being limited to one of these two parallel processes.

Our data suggest, therefore, that the principal locus of action of these noradrenergic agents is on processes occurring between 100 and 200 ms poststimulus. Because the latency of the earliest component, N100, was unaffected, it implies no noradrenergic modulation of antecedent primary auditory sensory afferents serially linked to this exogenous component. The fact that the timing of only some ERP components subsequent to the N100 were altered supports the idea of later parallel processing. One parallel set of processing tasks entails the evaluation and classification of stimuli according to their target status. This aspect of stimulus evaluation can be linked specifically to the N250. This is the earliest component for which a differential response to the target can be observed and its amplitude clearly denoted the target status of the evoking stimulus, as distinct from low probability. It has been suggested, previously, that N250 latency is the best index of the time required to evaluate an auditory stimulus (Grillon et al., 1990), and, in our data, increasing the difficulty of the target discrimination selectively delayed the latency of this component. The fact that medication had no effect on the latency of either N250 or the subsequent target-dependent P3b argues for the absence of direct noradrenergic modulation of cognitive processes specifically devoted to the evaluation of stimulus content. The Medication \( \times \) Task Difficulty interaction effect for N250 amplitude, independent of latency, suggests an indirect downstream alteration in the amount of neuronal activation required to complete this stimulus evaluation process; greater activation is required to classify relatively easy stimuli following clonidine and, conversely, less activation is required to classify more difficult stimuli following yohimbine. This ERP change is consistent with that observed for task performance.

A parallel set of processes, separate from N250 and P3b, are represented by the P200 and P3a ERP components. In contrast to N250 and P3b, the latencies of these components are altered in tandem by clonidine and yohimbine, suggesting that (a) P200 and P3a represent evaluative processes that are serially linked to each other, and (b) they are modulated directly by norepinephrine. The idea that the P3a subcomponent is elicited by novel or rare stimuli, independent of task significance, is reinforced by the fact that the two infrequent tones had equal P3a amplitudes, even though only one had target salience. This is in contrast to the P200, which is elicited in a comparable manner by all tones, both standard and rare. The P200-P3a complex may be understood, therefore, as a sequential process in which the P200 reflects early stimulus evaluation and the P3a reflects subsequent orienting towards and further categorization of those stimuli that exhibit deviance. Our results suggest that norepinephrine selectively enhances these physiological processes underlying the evaluation of novelty. They thus provide support for the idea that there is a noradrenergically modulated physiological mechanism that "tunes" the CNS to selectively attend to potentially important alterations in ongoing background stimulation. This is consistent with the overall notion that increased arousal tends to narrow the focus of attention (Eysenck, 1982). It is also consistent with a specific model of the noradrenergic system as functioning to maintain concentration and efficient cognitive functioning under conditions of stress or arousal, by preserving the discriminative selectivity of responses (AstonJones et al., 1994; Robbins & Everitt, 1987).
Noradrenergic agents, however, are not unique in affecting cognitive processes indexed by ERPs. Among the various neurotransmitters, GABA and acetylcholine, in particular, have been shown to have robust and consistent effects on P300 latency and amplitude (Frodl-Bauch, Bottlender, & Hergl, 1999). The inhibitory actions of sedating GABA agonists reduce P300 amplitude (Reinse1 et al., 1991; Rockstroh, Elbert, Lutzenerberger, & Altenmuller, 1991) and prolong P300 latency (Dominio, French, Pohorecki, Galus, & Pandit, 1989; Ray, Meador, & Loring, 1992). Cholinergic agonists, in contrast, enhance P300 amplitude, whereas antagonists decrease amplitude and delay latency (Diers, Frolich, Ihl, & Maurer, 1994; Hammond, Meador, Aung-Din, & Wilder, 1987; Meador et al., 1987). This is consistent with the augmenting effects of cholinergic agents on memory and cognition (Mohs & Davies, 1985). Catecholamines, though, have tended to show less robust effects. Pharmacologic probe and lesion studies have both suggested that dopamine contributes little to P300 generation and has robust effects. Pharmacologic probe and lesion studies have both suggested that dopamine contributes little to P300 generation and intact P3b exists in the healthy siblings of patients with schizophrenia (Turetsky et al., 1998). A similar profile of normal P3a and intact P3b exists in the healthy siblings of patients with schizophrenia (Turetsky, Cannon, & Gur, 2000). Collectively, these data suggest that P200 and P3a ERP abnormalities may be physiologic markers for a positive-symptom subtype of schizophrenia, for which there is evidence of familial linkage. The current findings raise the possibility that the information-processing deficits observed in these patients may reflect functional impairments of the noradrenergic neurotransmitter system.

Although not unequivocal, there is substantial evidence to support a role for norepinephrine in both state and trait aspects of schizophrenic psychopathology (van Kammen & Kelley, 1991). Increased norepinephrine levels have been found in the cerebrospinal fluid (Kemali, Del Vecchio, & Maj, 1982; Lake et al., 1980), as well as elevated plasma MHPG elevations both chronically and during periods of acute psychosis (Ko et al., 1988; van Kammen et al., 1990). Clonidine challenge studies have similarly revealed a blunted plasma MHPG lowering (Sternberg et al., 1982). As has been previously noted, however (Glazer, Charny, & Heninger, 1987), the data regarding noradrenergic dysfunction in schizophrenia are consistent overall, with the idea of a selected subtype abnormality. That is, noradrenergic disturbances are generally not ubiquitous but, rather, are seen in a subset of patients with schizophrenia (Holmberg & Gershon, 1961; Rosen, Silk, Rice, & Smith, 1985; Sternberg et al., 1981; Thibaut et al., 1998). The current study, relating ERP abnormalities to noradrenergic activity, provides a bridge between these two independent findings. It suggests that P200 and P3a abnormalities in schizophrenia might serve as indices of a physiologically distinct patient subtype that would benefit from clinical interventions directed toward the noradrenergic system (Freedman et al., 1982; Jimerson, Post, Stoddard, Gillin, & Bunney, 1980).

### REFERENCES


$\alpha_2$-Adrenergic effects on auditory processing


