Noise Stress Impairs Prefrontal Cortical Cognitive Function in Monkeys

Evidence for a Hyperdopaminergic Mechanism

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**Background:** Stress can exacerbate a number of psychiatric disorders, many of which are associated with prefrontal cortical (PFC) cognitive deficits. Biochemical studies demonstrate that mild stress preferentially increases dopamine turnover in the PFC. Our study examined the effects of acute, mild stress exposure on higher cognitive function in monkeys and the role of dopaminergic mechanisms in the stress response.

**Methods:** The effects of loud (105-dB) noise stress were examined on a spatial working memory task (delayed response) dependent on the PFC, and on a reference memory task with similar motor and motivational demands (visual pattern discrimination) dependent on the inferior temporal cortex. The role of dopamine mechanisms was tested by challenging the stress response with agents that decrease dopamine receptor stimulation.

**Results:** Exposure to noise stress significantly impaired delayed-response performance. Stress did not impair performance on “0-second” delay control trials and did not alter visual pattern discrimination performance, which is consistent with impaired PFC cognitive function rather than nonspecific changes in performance. Stress-induced deficits in delayed-response performance were ameliorated by pretreatment with drugs that block dopamine receptors (haloperidol, SCH 23390) or reduce stress-induced PFC dopamine turnover in rodents (clonidine, naloxone hydrochloride).

**Conclusions:** These results indicate that stress impairs PFC cognitive function through a hyperdopaminergic mechanism. Stress may take the PFC “off-line” to allow more habitual responses mediated by posterior cortical and subcortical structures to regulate behavior. This mechanism may have survival value, but may often be maladaptive in human society, contributing to the vulnerability of the PFC in many neuropsychiatric disorders.

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SUBJECTS AND METHODS

SUBJECTS
The subjects were 8 young adult (≈4-9 years) rhesus monkeys (Macaca mulatta; 6 female, 2 male). All animals were housed individually under standard laboratory conditions. Animals were fed monkey chow and fruit immediately following testing.

COGNITIVE TESTING
Cognitive testing was conducted in a Wisconsin general testing apparatus with background masking noise (60 dB, wideband frequency). Highly palatable rewards (e.g., raisins) were used to minimize the need for dietary regulation. The monkeys were tested twice a week (Mondays and Thursdays).

Delayed-Response Task
During delayed response, the animal watches as the experimenter places 1 of 2 food wells. The food wells are then covered with identical cardboard plaques and an opaque screen is lowered for a specified delay. The screen is then raised and the animal responds. Reward is quasi-randomly distributed between the left and right wells during the 30 trials that comprise a daily test session.

To observe effects on memory capacity, the animals were trained on a variable delayed-response task in which the delays varied between less than 1 second (0 seconds) and the temporal interval that produced performance near chance levels for each animal within a session. Five different delay lengths (designated A, B, C, D, and E delays) were quasi-randomly distributed during the test session; e.g., delays for monkey 443 were 0, 10, 20, 30, and 40 seconds. All monkeys performed near perfectly at 0 seconds and exhibited increasing difficulty with longer delays. Delays were adjusted until the animals showed a stable baseline performance of approximately 80% correct, thus allowing room for either improvement or impairment in performance.

Visual Pattern Discrimination Task
The visual pattern discrimination task was similar to the delayed-response task in that animals had to displace the correct cardboard plaque to uncover a food reward. However, in this reference memory task, food reward was always associated with one visual pattern (black background with a white cross) and not with the other (black with a white square). Spatial position was irrelevant, varying quasi-randomly across the 30 trials. The intertrial interval was 10 seconds. Stress exposure occurred after the animals had achieved a stable baseline performance of about 90% correct.

STRESS EXPOSURE
Mild stress exposure consisted of continuous loud noise (100-110 dB, wide-band frequency) for 30 minutes prior to the testing procedure. Pilot experiments showed that presenting the noise before testing was as effective as presenting the noise stress during testing (before, −18.0%±2.9%; during, −23.5%±5.4%), but did not have the potential confound of distracting the animal. Performance under stressful conditions was compared with performance under control conditions (background masking noise, 60-70 dB) earlier that week. Noise levels in the testing chamber were verified with a decibel meter. This stressor has been shown previously to increase cortisol release in both monkeys and humans. To control for any habituation to this mild stressor, half the animals were exposed to the noise stress for the first time prior to visual discrimination testing, while the remaining animals were exposed to the noise for the first time prior to delayed-response testing. These methods were approved by the Yale Animal Care and Use Committee, New Haven, Conn.

DRUG ADMINISTRATION
Drug solutions were made fresh each day under aseptic conditions. Drug solution (0.04-mg/kg clonidine, 0.3-mg/kg naloxone hydrochloride, 0.003- to 0.03-mg/kg haloperidol, or 0.01- to 0.1-mg/kg SCH 23390) or sterile saline solution was injected intramuscularly 1 hour prior to testing. Doses of clonidine and naloxone were based on previous work with these compounds in monkeys and humans. The experimenter testing the animal was blinded to the drug treatment conditions. Drug administration occurred only after an animal had returned to baseline performance for 2 consecutive test sessions. Therefore, all washout periods between drug injections were at least 10 days.

Pilot studies indicated that animals habituated rapidly to the mild stressor if stress sessions occurred close together in time (e.g., monkey 414: first stress exposure, −17%; next stress exposure 2 weeks later, 0% compared with saline solution control). Thus, the study of drug pretreatment on the stress response required 2 additions to the experimental design. First, stress sessions were separated by at least 3 months. Second, stress sessions with saline solution both preceded and proceeded stress sessions with drug solution (stress session with saline solution; 3 months later, stress session with drug solution; 3 months later, stress session with saline solution) and the response with drug was compared with the average of the 2 saline sessions. Using these conservative methods, an average of approximately 9 months was needed to acquire each drug/stress data point.

DATA ANALYSIS
Delayed-response performance following stress or drug treatment was compared with matched saline solution control performance for the same week. As described earlier, performance on stress sessions with drug was compared with the average of the stress sessions with saline preceding and proceeding the drug session. Statistical analyses used repeated-measures designs: analysis of variance (ANOVA) with repeated measures for multiple comparisons and paired t tests (dependent t test [t-dep]) for single comparisons (P<.05, 2 tailed). Statistical analysis was conducted on a Macintosh computer using Systat (Systat Inc, Evanston, Ill). Data are given as means±SEM.

Our study examined the effects of mild stress exposure on higher cognitive function in monkeys, using the same stressor employed in human studies, continuous loud white noise (100-110 dB). Prefrontal cortex cognitive function...
was assessed using the delayed-response task, a test of spatial working memory that critically depends on the dorsolateral PFC.34 A variable-delay paradigm was used, including trials with 0-second delays to examine potential changes in performance unrelated to working memory. The effects of stress were also examined on a control task, visual pattern discrimination, which is not sensitive to PFC lesions35 but rather depends on the inferior temporal cortex and its connections to striatum.36,37 The role of DA mechanisms in the stress response were explored by challenging with pharmacological agents that either (1) prevent the rise in stress-induced DA release in the PFC (such as clonidine and naloxone) or (2) block DA receptors (such as haloperidol, a nonselective DA receptor antagonist, and SCH 23390, a selective D1 receptor antagonist).

RESULTS

THE EFFECTS OF NOISE STRESS ON DELAYED RESPONSE VS VISUAL PATTERN DISCRIMINATION PERFORMANCE

Exposure to stressful levels of noise for 30 minutes before testing significantly impaired delayed-response performance (Figure 1; n=5, 2-way ANOVA with repeated measures on factors of stress and delay: effect of stress, F1,4=119.6, P<.001; effect of delay, F1,4=293.0, P<.001; stress × delay interaction, F1,4=6.64, P=.06). Stress did not impair performance on trials with 0-second delays (F1,4=0.98, P=.38; Figure 1), but did impair performance when non–0-second delays were used (F1,4=28.0, P=.006; Figure 1). This response pattern is consistent with stress impairing PFC cognitive function rather than non-specific alterations in performance variables such as impaired motivation or motor performance. A more detailed analysis of stress effects on performance following different delays showed that stress impaired performance at both short and longer delays, a pattern consistent with impaired PFC cognitive function (Table 1; shortest to longest delays: B delay, F1,4=23.14, P=.009; C delay, F1,4=5.56, P=.08; D delay, F1,4=9.85, P=.04; E delay, F1,4=0.06, P=.81).

Consistent with this interpretation, stress exposure did not alter performance of the visual pattern discrimination task, a test that does not depend on the functional integrity of the PFC yet has similar motor and motivational demands as delayed response (Figure 2; n=3, control vs stressful noise conditions: t-test=2.98, df=2, P=.02). Comparisons of stress effects on delayed response vs visual pattern discrimination performance were significant (independent t test = 2.98, df=7, P=.02).

THE EFFECTS OF CLONIDINE OR NALOXONE PRETREATMENT ON THE STRESS RESPONSE

As clonidine and naloxone have been shown to prevent the rise in stress-induced DA turnover in rodent PFC,21,23 we examined the effects of these agents on stress-induced cognitive impairment in monkeys. Using a 3-month separation between stress sessions, monkeys continued to show impaired delayed-response performance following stress exposure with saline solution pretreatment (average saline control performance, 83.3±1.3%...
Correct; average saline stress session performance, 70.1%±2.9% correct; n=6; t-dep=7.3, df=5, P<.001). Administration of clonidine (0.04 mg/kg) did not alter delayed-response performance under control (nonstress) conditions (saline control, 81.0%±7.5% correct; clonidine control, 82.0%±9.1% correct). However, clonidine pretreatment significantly reversed the harmful effects of stress exposure (average saline solution stress session performance, 66.7%±7.4% correct; clonidine stress session performance, 84.7%±5.4% correct; n=3; t-dep=21.00, df=2, P=.002). A similar, although slightly weaker, response pattern was observed with naloxone hydrochloride (0.5 mg/kg) pretreatment. Naloxone by itself had no effect on performance (saline control performance, 80.0%±4.2% correct; naloxone control performance, 78.0%±7.1% correct), but significantly reversed the effects of stress (average saline stress session performance, 66.2%±8.3% correct; naloxone stress session performance, 78.3%±7.1% correct; n=3; t-dep=4.35, df=2, P=.05). Individual responses to drug are presented in Table 2.

**Table 2. Effects of Drug Pretreatment on the Stress Response in Individual Animals**

<table>
<thead>
<tr>
<th>Monkey</th>
<th>Saline</th>
<th>Clonidine</th>
<th>Monkey</th>
<th>Saline</th>
<th>Naloxone Hydrochloride</th>
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</table>

*Results represent percent change from matched saline control performance; the saline stress response represents the average of the saline stress sessions before and after drug stress testing. Ellipses indicate not applicable.

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**Figure 3.** Dopamine (DA) receptor antagonist pretreatment reverses the detrimental effects of stress exposure. Results represent means±SEM percent correct on the delayed-response task (collapsed across both delay and no delay conditions); the horizontal line indicates mean response following vehicle pretreatment with control (CON) noise conditions. The response to noise stress (STR) represents the mean of all exposures. Either DA antagonist pretreatment or stress exposure by itself impaired performance; the combined treatments normalized performance. These results are consistent with either insufficient (DA antagonist) or excessive (stress) DA receptor stimulation in the prefrontal cortex impairing prefrontal cortical function. CON indicates control noise conditions; STR, mild stress conditions; SCH, SCH 23390 pretreatment; HAL, haloperidol pretreatment; and VEH, vehicle pretreatment. Asterisk indicates significantly different from vehicle/control; dagger, significantly different from vehicle/noise stress.

**Table 3.** Summary of results for each animal and condition. Each animal received a 0.005-0.01 mg/kg dose of SCH 23390 or haloperidol (0.01-0.1 mg/kg). Haloperidol doses of 0.01-0.03 mg/kg did not restore normal levels of delayed-response performance in stressed monkeys (Figure 4, D; stress session with saline vs stress session with haloperidol, n=3; t-dep=0.5, df=2, P=.67). These higher haloperidol doses produced signs of mild motor impairment (eg, mild bradykinesia, dystonia, errors at 0-second delays) when administered under nonstressful conditions (Figure 4, C). Under nonstressful, control noise conditions, 1 monkey refused to test following the 0.03-mg/kg dose, and the 0.01-mg/kg dose reduced delayed-response performance to chance levels of responding (saline control, 82.1%±1.5% correct; haloperidol control, 52.0%±6.0% correct).

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**Comment**

Our study is limited by the global nature of the manipulations; both stress and systemic drug administration have effects throughout the nervous system. However, the pattern of response, in concert with results from related stud-
ies, suggests that acute, mild stress can impair PFC function through a hyperdopaminergic mechanism.

**EVIDENCE FOR PFC DYSFUNCTION**

Acute exposure to loud noise impaired performance of a spatial working memory task dependent on the PFC. This stressor had no effect on performance following 0-second delay control trials. Similarly, no motor deficits were observed following a 0.005-mg/kg dose of haloperidol. The effects of 0.005 mg/kg of haloperidol vs saline vehicle pretreatment on delayed-response performance under control vs stressful noise conditions. Results (percent correct) are shown for performance at each delay length. This low dose of haloperidol impaired performance at longer delays but had no effect on 0-second delay control trials. Similarly, no motor deficits were observed following a 0.005-mg/kg dose of haloperidol. The effects of 0.005 mg/kg of haloperidol vs saline vehicle pretreatment on delayed-response performance under control vs stressful noise conditions. Results (percent correct) are shown for performance at each delay length. This low dose of haloperidol impaired performance following 0-second delays as well as longer delays and produced very mild motor deficits. The effects of 0.01 mg/kg of haloperidol vs saline vehicle pretreatment on delayed-response performance under control vs stressful noise conditions. Results (percent correct) are shown for performance at each delay length. This higher dose of haloperidol did not restore normal levels of responding during stress.

**Figure 4.** The effects of low (0.005-mg/kg) vs higher (0.01-mg/kg) doses of haloperidol on delayed-response performance under control vs stressful noise conditions in monkey 442. A, The effects of haloperidol (0.005 mg/kg) vs saline on delayed-response performance under control noise conditions. Results (percent correct) are shown for performance at each delay length. This low dose of haloperidol impaired performance at longer delays but had no effect on 0-second delay control trials. Similarly, no motor deficits were observed following a 0.005-mg/kg dose of haloperidol. B, The effects of 0.005 mg/kg of haloperidol vs saline vehicle pretreatment on delayed-response performance under control vs stressful noise conditions. Results (percent correct) are shown for performance at each delay length. This low dose of haloperidol impaired performance following 0-second delays as well as longer delays and produced very mild motor deficits. C, The effects of haloperidol (0.01 mg/kg) vs saline on delayed-response performance under control noise conditions. Results (percent correct) are shown for performance at each delay length. This higher dose of haloperidol impaired performance following 0-second delays as well as longer delays and produced very mild motor deficits. D, The effects of 0.01 mg/kg of haloperidol vs saline vehicle pretreatment on delayed-response performance under control vs stressful noise conditions. Results (percent correct) are shown for performance at each delay length. This higher dose of haloperidol did not restore normal levels of responding during stress.

Selective dysfunction of the PFC during stress may have survival value, favoring well-rehearsed or instinc- tual behaviors regulated by subcortical structures and posterior cortex rather than slower, more complicated PFC regulation. However, these mechanisms may be mal-adaptive in human society when PFC functions (eg, work-
ing memory, behavioral inhibition, mental flexibility, and concentration) are necessary for appropriate behavioral regulation.

EVIDENCE FOR A HYPERDOPAMINERGIC MECHANISM

Does increased DA release in the PFC during stress exposure underlie the impairments in working memory performance? This hypothesis was tested by challenging the stress response with pharmacological agents that either decrease stress-induced DA release or block DA receptors. Both strategies successfully reversed the stress response. As these treatments by themselves either had no effect on performance (clonidine, naloxone), or impaired performance (haloperidol, SCH 23390), simple additive effects cannot account for their ability to improve stress-induced cognitive impairment. Instead, these results suggest that stress elicits excessive DA release, which can be normalized by reducing DA receptor stimulation. This interpretation is consonant with recent results showing that a pharmacological stressor, FG 7142, similarly impairs spatial working memory performance in rats or monkeys,22,29,30 and that the degree of impairment correlated with the increase in PFC DA turnover.29,30 Most recently, we have shown that DA D1-receptor infusion into the PFC mimics the stress response,33 demonstrating that increased DA D1-receptor stimulation in the PFC is sufficient to induce working memory deficits. Conversely, the finding that DA antagonists impair cognitive performance (current study)27,28 indicates that there is a narrow range of optimal DA stimulation for proper PFC function, and that either too little (DA receptor blockade) or too much (stress exposure) DA receptor stimulation impairs PFC function. Similar results have been observed at the cellular level, where PFC neurons also have been shown to exhibit an inverted U response to D1-receptor stimulation.31

Norepinephrine, serotonin, and acetylcholine systems also respond to stress, although in the PFC, DA appears to be the most responsive.52 Do these systems contribute to stress-induced working memory deficits? To date, manipulations of the serotonergic30 or muscarinic (J. D. Jentsch, unpublished data, 1995) systems do not seem to ameliorate stress-induced working memory deficits, but more intensive investigation is needed. However, high levels of norepinephrine release may impair PFC working memory abilities via an α1-receptor mechanism,53 suggesting that catecholamines may interact to take the PFC “off-line” during stress.

RELEVANCE TO NEUROPSYCHIATRIC DISORDERS

Exposure to stress is thought to exacerbate or precipitate a number of neuropsychiatric disorders, including schizophrenia, depression, and attention-deficit/hyperactivity disorder.1 Although these are distinct disorders, all involve PFC cognitive deficits.44-48 The current finding of an active neurochemical mechanism that takes the PFC “off-line” during mild stress suggests a possible explanation for the vulnerability of the PFC in many mental disorders.

Results from this study and others suggest that α2-adrenergic agonists22,49 or very low doses of DA receptor antagonists30,32 may be useful in treating stress-related PFC cognitive impairment. However, our study cautions that slightly larger doses of haloperidol may be too high for restoring cognitive function. It is important to note that these “high” doses of haloperidol (0.01-0.03 mg/kg) are still at the very low end of the clinical dose range (about 0.01-0.1 mg/kg). A similar pattern has recently been observed with clozapine, an atypical neuroleptic.50 Higher doses of neuroleptics may be ineffective owing to excessive blockade of DA receptors in the PFC or impaired striatal function producing response deficits. Treatment with neuroleptics such as haloperidol does not ameliorate PFC cognitive deficits in patients with schizophrenia,51 leading many researchers to speculate that DA activity may be underactive in the PFC of schizophrenic patients.52-54 However, the current data suggest an alternative explanation: the doses of neuroleptic drugs needed to treat the positive symptoms of schizophrenia may simply be too high to restore optimal PFC function. This interpretation is supported by the finding that schizophrenic patients, like the monkeys in the current study, show an inverted U dose-response curve to DA treatments when performing a PFC task (word fluency).55 Further research is needed to determine whether detrimental DA actions contribute to PFC cognitive deficits in patients as they do in animal studies.

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