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INTERNATIONAL
JOURNAL OF
PSYCHOPHYSIOLOGY

International Journal of Psychophysiology 36 (2000) 59–68

www.elsevier.com/locate/ijpsycho

Modulation of attentional inhibition by norepinephrine and cortisol after psychological stress

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Received 7 June 1999; received in revised form 4 November 1999; accepted 8 November 1999

Abstract

Two of the most salient physiological responses to stress are increased norepinephrine (NE) and cortisol (CORT) activities. However, it is unclear how these neurochemical events affect cognition, especially attention. We examined the effects of mild psychological stress on selective attention, as assessed by the negative priming (NP) paradigm. Salivary measures of the stress hormone CORT and α -amylase (a correlate of NE) were assayed to probe the relationship between the stress response and attentional inhibition. Healthy subjects ($N=20$) engaged in the attention task, which was then followed by 15 min of a stressful video game before a return to the attentional task. Baseline saliva samples were obtained before the experiment began, 1 min after the video-game stressor, and 20 min post-stress. Subjects showed a significant reduction in NP and a decrease in reaction time (RT) after the video game. Moreover, α -amylase levels increased significantly after the stressor, indicating the role of NE in the acute stress response. While CORT levels remained unchanged after stress, CORT correlated significantly with both NP scores and RT after the stressor. These results imply that mild psychological stress can significantly alter attentional processes. Given the increase in α -amylase and the correlation between attention and CORT after stress, it seems likely that attentional processes are under tight control by brain systems which mediate the fight-or-flight response. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Stress; Attention; Norepinephrine; Cortisol; α -amylase; Negative priming

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PII: S0167-8760(99)00100-2

1. Introduction

The central nervous system component of the stress response can be conceptualized as occurring in two stages: a short latency catecholamine component which represents the first wave, and a slower acting glucocorticoid response representing the second wave. The first wave of the mammalian 'flight or fight' response depends upon the release of the catecholamine neurotransmitter norepinephrine (NE; Thierry et al., 1968; Korf et al., 1973; Cassens et al., 1980). More specifically, stressors such as footshock, hypotension, hypoxia, and visceral stimulation increase the discharge rates of the locus coeruleus (LC), the main source of NE afferents to the rest of the brain (Cedarbaum and Aghajanian, 1978; Elam et al., 1981, 1984; Abercrombie and Jacobs, 1987a,b; Morilak et al., 1987; Svensson, 1987). Such changes in the firing rates of LC neurons occur within seconds of the administration of stress, and in turn project to areas such as the hypothalamus, cerebral cortex, and hippocampus, initiating a full blown stress response (Segal and Bloom, 1976; Rogawski and Aghajanian, 1980; Waterhouse and Woodward, 1980).

The second wave of the stress response occurs when the glucocorticoid cortisol (CORT) is released by the adrenal cortex (Hennessy and Levine, 1979). CORT has a longer latency of release than does NE (minutes instead of seconds), and it can take hours for the adaptive effects to emerge. CORT's mechanism of action involves the modification of transcriptional events via Type I and Type II CORT receptors. These receptors represent intracellular DNA binding proteins, and serve to modulate protein synthesis within the cell (McEwen et al., 1986). Hence, while NE activity is immediately increased in response to threatening stimuli, CORT modulates the long-term neuronal changes associated with stress.

Based on the neuroanatomical localization of the stress-response systems, it has been hypothesized that stressful stimuli can affect information processing, especially memory and attention. For example, Callaway and Thompson (1953) suggested that any stressor which induced sympa-

thetic arousal would serve to raise the input threshold of incoming stimuli in order to prevent sympathetic discharge from reaching intolerable limits (i.e. a negative feedback loop). Thus, stress would actually narrow the focus of attention, and several studies initially provided evidence for such an effect (Kohn, 1954; Callaway and Dembo, 1958; Callaway, 1959; Agnew and Agnew, 1963).

However, contradictory findings have been obtained from both human and animal studies. In an attempt to elucidate the neurochemical underpinnings of the effect of stress on cognition, several groups have shown that NE depletion in rodents and monkeys can cause both increased distractibility and spatial working memory deficits (Roberts et al., 1976; Brozoski et al., 1979; Carli et al., 1983). Furthermore, it has been repeatedly demonstrated that the administration of α_2 -NE agonists improves performance on such tasks (Arnsten et al., 1988; Arnsten and Leslie, 1991; Arnsten and Contant, 1992; Cai et al., 1993). Given that NE activity is increased during stress and that recent electroencephalographic (EEG) data in humans demonstrate that stress causes deficits in attentional processes (Attias et al., 1996; Mölle et al., 1997; White and Yee, 1997), earlier results showing improvements in attention observed during NE agonist administration appear contradictory. Thus, it is still unclear what role what NE plays in relation to stress and cognition.

One possible explanation for the disparate results found in relation to NE and cognition is that CORT is a more salient modulator of information processing after stress than is NE. For example, one particularly reliable phenomenon is the fact that acute stress can enhance memory formation while chronic stress can attenuate it (McEwen and Sapolsky, 1995). It has been demonstrated that this effect is conditional upon CORT release and the differential occupation of Type I vs. Type II CORT receptors in the hippocampus (McEwen and Sapolsky, 1995). In addition, it has also been shown that there is a negative correlation between CORT levels and measures of selective attention in normal human subjects (Lupien et al., 1994). Thus, it appears that CORT may be an important key to understanding how stress affects cognition.

One important way in which stress may affect attention is through inhibitory mechanisms. The negative priming (NP) paradigm is designed to assess the role of inhibition in selective attention (Tipper, 1985). NP is structurally similar to the phenomenon of latent inhibition (Lubow, 1973) and involves exposing subjects to stimuli that are to be initially ignored and subsequently selected. It is hypothesized that selective attention is achieved by at least two mechanisms: an excitatory process associated with the selected target stimulus, and an inhibitory process associated with the ignored distractor stimulus (Neill and Westberry, 1987). In the visuospatial NP task, pairs of prime and probe displays are presented. First, a 'prime' display is presented in which a target stimulus must be located while a distractor stimulus is ignored. Immediately following the 'prime' display, a 'probe' display is presented, in which a target stimulus is presented at the ignored distractor position from the previous prime display (i.e. ignored repetition). Thus, subjects are required to select the location that they had just ignored. Typically, when a 'prime'–'probe' pair involves such an ignored repetition, the reaction times (RTs) to locate the target on the 'probe' displays are longer owing to inhibitory processes associated with the ignored location. Such an increase in RT as a result of a previous exposure is called the negative priming effect. In the ignored repetition condition, the negative priming effect depends on the degree of selective attention achieved on the prime display. Hence, the greater the attentional inhibition, the slower the RT to locate the target on the subsequent probe display. When the 'prime'–'probe' pairs do not involve an ignored repetition of a location, such increases in RTs to locate the target on the probe displays do not occur. In other words, when the location of the distractor in the 'prime' display and the location of the target in the 'probe' display do not overlap, there is no NP effect.

The purpose of the present study was to examine the effects of mild psychological stress on performance of a visuospatial NP task and on CORT and NE levels in healthy human subjects. The stressor utilized was video game play, which

has been shown to elicit stress responses including increased heart rate, blood pressure, decreased RT, and the induction of seizures (Glista et al., 1983; Gwinup et al., 1983; McSwegin et al., 1988; Segal and Dietz, 1991; Modesti et al., 1994; Griffiths and Dancaster, 1995; Yuji, 1996). In order to rule out the confound of additional stress induced by blood or urine collection, NE activity was assayed non-invasively utilizing salivary α -amylase levels, which have recently been shown to correlate with plasma NE concentration, and are increased by physical and psychological stress (Chatterton et al., 1996). Cortisol was also assayed utilizing salivary measures.

2. Methods

2.1. Subjects

Participants were 20 (50% male) healthy young adults, aged 18–24 (mean = 21.3 years). They were recruited by flyers posted on the campus of Northwestern University. Potential subjects were screened for a history of drug use, mental illness, and head injury. Questionnaires administered prior to testing indicated that no subjects consumed alcohol within 24 h, consumed caffeine or nicotine, or engaged in strenuous physical activity the day of testing. Care was taken to run each subject at the same time of day (afternoons) to eliminate the confound of diurnal fluctuations in plasma cortisol levels. Subjects were paid for their participation in the study.

2.2. Apparatus and stimuli

The stimuli were presented on a Macintosh computer. There were four locations on the screen where the target (o) or the distractor (+) could appear. The four positions were placed on the corners of an imaginary square. The visual angle between the horizontal or the vertical positions was 7.8° (see Fig. 1). The stimuli (o or +) subtended 0.6 by 0.6° of visual angle. Subjects sat 45 cm from the screen. Each trial was started by the

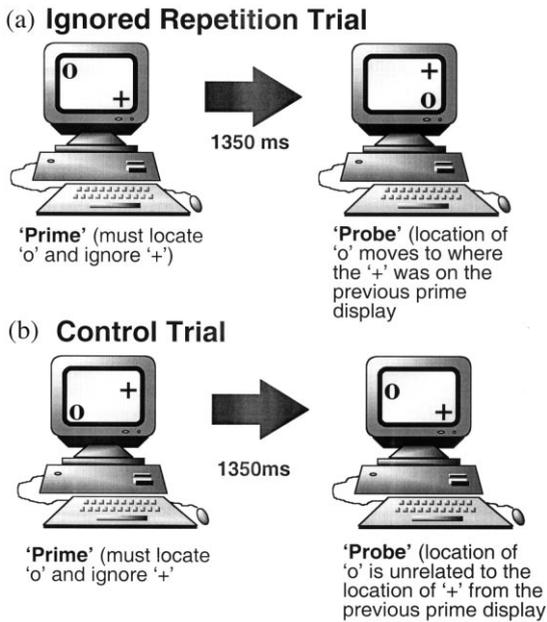


Fig. 1. Schematic diagram of the sequence of stimuli presented in each NP trial. Neutral trials which lacked a distractor on the prime display are not shown.

experimenter only when the subject was fixating in the center.

2.3. The negative priming task

There were three types of trial involving 'prime'–'probe' display pairs: (1) *ignored repetition trials* (IR) represented the condition in which the RTs to locate the target on the probe were expected to be slowed; (2) *control trials* (C) in which the target position on the probe display was unrelated to the distractor position in the prime display; and (3) *neutral trials* (N) characterized by an absence of a distractor in the prime displays (not shown). N trials were utilized to assess the simple RT to detect a visual target. C trials served as the baseline upon which to measure the changes in RT exhibited in IR trials. The dependent measure was the reaction time to locate the target on the probe trials. NP scores were calculated by subtracting the IR probe RTs from the C probe RTs. Thus, longer RTs in the IR trials as compared to those from the C trials resulted in more

negative NP scores, and indicated a greater NP effect (greater attentional inhibition).

2.4. Stressor stimuli

Video game play served as the stressor in the present experiment. The video game subject matter fell into the category of 'human violence' as described previously (Funk, 1993) and the participants had little or no prior experience with the particular game used. Subjects were seated in front of the computer monitor and were explained the rules of the game. The game objective was to kill as many enemy characters as possible before being killed. The game layout took on a first person perspective which provided a level of virtual realism. Stereo headphones were also utilized to add to the realistic nature of the stressor. Subjects engaged in video game play for 15 min and were allowed to play as many games as possible within the allotted time.

2.5. Procedure

All participants signed an informed consent form prior to the start of the experiment. A within subjects design was utilized in which the participants performed one 20-min block of the NP task, engaged in video game play for 15 min, and then performed a second 20-min block of the NP task. Subjects were seated in front of the computer and were asked to read the instructions on the screen. Subjects were told that they must pay attention to the target and ignore the distractor. They were asked to indicate the location of the target o by pressing the corresponding key on a keyboard. They were asked to identify the target as quickly as possible. Subjects initiated a block of trials by pressing the spacebar. There were 72 trials per block [i.e. 72 pairs of prime and probe displays or 24 ignored repetition trials, 24 control trials, and 24 neutral trials (Fig. 1)]. A trial began with a center fixation point and then a prime display which stayed on until the subject responded to it by locating the target. Then, there was a 1350-ms pause before the second display (probe) was presented. During the final 800 ms of

the pause, the fixation point reappeared at the center to prepare subjects for the next response. When the subject responded to the probe display by locating the target, a pattern mask was presented and stayed on the screen. At this point, the subjects were asked if they were ready to go on to the next trial. When ready, the subject pressed the spacebar, after which there was always at least a 6.4-s delay before the next trial was presented. During the last 800 ms of the pause the fixation point appeared at the center to prepare the subject for the next prime display. The order of presentation of the different types of trial was random within each block. The entire procedure took approximately 1 h per subject.

Saliva samples (2.5 ml) were collected at the start of the experiment, immediately after the stressor, and 20 min after playing the video game. Subjects were asked to spit approximately 2 ml of saliva into a 50-ml graduated conical test tube. Saliva was then kept at -20°C until the biochemical assays were performed.

2.6. α -Amylase assay

Assay kits, obtained from Sigma Chemical Co., utilized maltotetraose as substrate with NAD, maltose phosphorylase, β -phosphoglucomutase, and glucose-6-phosphate dehydrogenase in a phosphate buffer. The formation of NADH was measured after 2 min by its absorption at 340 nm in a spectrophotometer. Saliva was diluted 1:2000 in 0.15 mol/l sodium chloride before addition to the substrate for the assay. The quality control for the assay was prepared from a pool of saliva that was collected from the participants. The pool was divided into 1.0-ml aliquots and was frozen in

sealed vials. One vial was thawed and run with each assay.

2.7. Cortisol assay

Salivary cortisol was assayed without extraction after a 1:10 dilution in 0.01 mol/l citrate buffer (pH 4.0). Antiserum was prepared in this laboratory. The cross-reacting steroids were 11-deoxycortisol (17.4%) and corticosterone (5.4%). All others tested cross-reacted $< 0.2\%$. The $[1,2-^3\text{H}]$ cortisol was obtained from New England Nuclear Division of DuPont Co., Boston, MA, USA.

2.8. Data analysis

NP scores, RTs, α -amylase levels, and cortisol levels before and after the stressor were examined utilizing a repeated measures analysis of variance (ANOVA) and Pearson product moment correlations. The criterion for statistical significance was $P < 0.05$, two-tailed.

3. Results

A summary of the results of the present study can be seen in Table 1. The accuracy in locating the target was close to 100% for nearly all the subjects, with an average error rate of less than 1%. This error rate was unaffected by administration of the video game stressor. Fig. 2a shows the effects of stress on NP scores (more negative scores on NP indicate greater attentional inhibition) and the simple RTs from the neutral trials (Fig. 2b). A repeated measures ANOVA indicated that subjects became attentionally disinhib-

Table 1
Mean (\pm S.E.) behavioral and physiological measures both before and after stress

	Baseline	After stress	
Reaction time (ms)	442.3 \pm 16.4	422.9 \pm 14.7	
Negative priming	-29.7 \pm 4.4	-8.0 \pm 8.1	
		1 min post-stress	20 min post-stress
Cortisol (ng/ml)	1.18 \pm 0.22	1.04 \pm 0.12	0.96 \pm 0.013
α -amylase (kU/l)	42.2 \pm 7.7	58.5 \pm 12.3	59.5 \pm 11.8

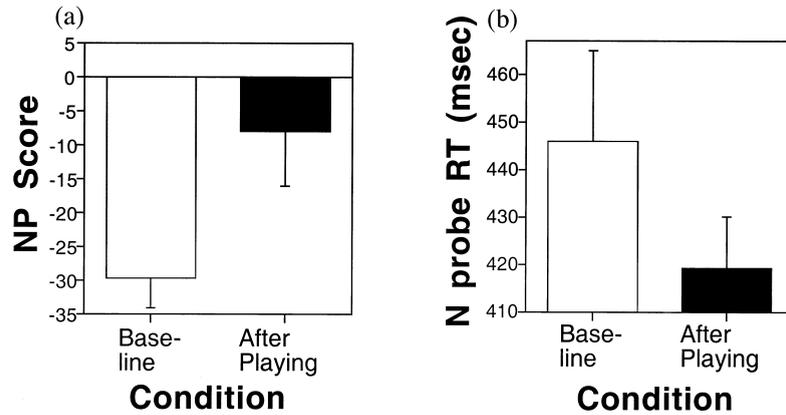


Fig. 2. (a) Mean NP scores and (b) RTs from the N probe trials both before playing the video game and after playing. Representative error bars indicates S.E.M. More negative scores indicate better NP (greater attentional inhibition) (a).

ited (i.e. NP effect was significantly reduced) after stress ($F_{1,19} = 5.54$, $P < 0.03$) (Fig. 2a). Reduced NP was not a result of an overall deterioration of visual attention because subjects were considerably faster at detecting single targets on the N trials after stress ($F_{1,19} = 7.74$, $P < 0.015$) (Fig. 2b). As can be seen in Fig. 3, the reduction of the NP effect was accompanied by an increase in NE activity, as indicated by the increase in salivary α -amylase levels after stress ($F_{2,38} = 3.4$, $P < 0.05$).

The salivary CORT levels showed no significant change from baseline over the same time period ($F_{2,38} = 1.4$, $P > 0.27$). However, the NP scores

after stress correlated significantly with CORT levels at 20 min post-stress ($r = 0.47$, $P < 0.05$) (Fig. 4a). In other words, those with higher CORT levels had a greater disruption of attentional inhibition since more positive NP scores indicate reduction in NP. The correlation between NP scores and CORT immediately after stress was at the trend level ($r = 0.30$, $P < 0.09$). Interestingly, there was a negative correlation between CORT levels and general RT immediately after stress but not at any other time ($r = -0.46$, $P < 0.05$) (Fig. 4b). There was no significant correlation between the changes in NP scores and the changes in CORT or NE levels.

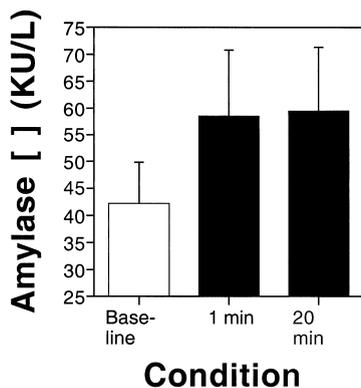


Fig. 3. (a) Mean salivary α -amylase (AA) concentrations before playing the video game, immediately following play, and 20 min after. Representative error bars indicate S.E.M. AA concentrations are measured in kilounits per liter.

4. Discussion

The results of the present study have demonstrated that even mild psychological stress can reduce attentional inhibition as evidenced by the change in NP scores after stress. Even though the subjects displayed a significant reduction in the ability to filter out irrelevant information after stress, general RT decreased which indicates that the decline in the NP effect was not do to an overall deterioration of visual attention. The current study also provided biochemical support for the hypothesis that neurochemical/neurohormonal stress-response systems can modulate

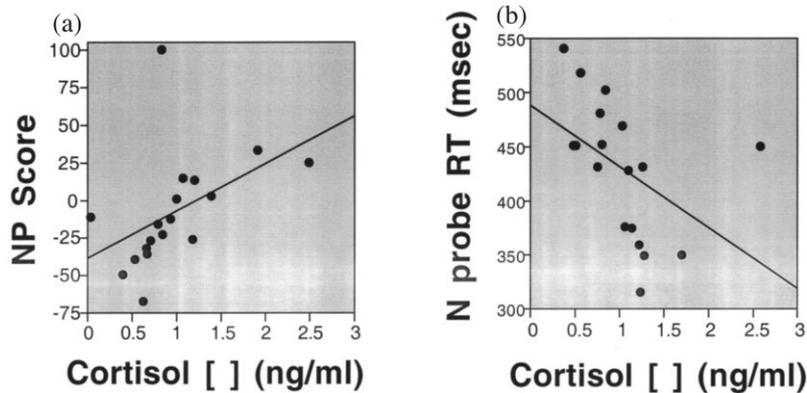


Fig. 4. (a) Correlation between salivary cortisol concentrations 20 min after play and NP scores after playing. All cortisol concentrations are measured in ng/ml. (b) Correlation between cortisol concentrations 1 min after play and neutral trial (N) RTs on probe displays.

the cognitive process of selective attention. Support for such an assertion comes from the fact that salivary α -amylase/NE levels increased in conjunction with the decreases seen in NP scores. Furthermore, there was a significant correlation between salivary CORT levels and NP scores 20 min post-stress, indicating that those subjects who had higher concentrations of CORT had greater reductions in attentional inhibition. Finally, CORT levels after stress correlated with general RT after stress, supporting the role of this hormone in general arousal.

While previous studies have shown that stress can alter attentional processes using such techniques as pre-pulse inhibition and event-related potentials (Attias et al., 1996; White and Yee, 1997), the present study was the first to demonstrate that stressful stimuli can disrupt attentional inhibition utilizing the NP paradigm. Such results validate both the ideas that stress can alter attentional processes and that the NP paradigm is a useful method with which to measure selective attentional inhibition.

The present study was also one of the first to examine the relationship between stress, NE/CORT response, and cognition in the same experiment. Previous studies have separately shown that: (1) stress increases NE/CORT release (Thierry et al., 1968; Korf et al., 1973; Hennessy and Levine, 1979; Cassens et al., 1980); (2) stress

can alter cognitive functioning (Attias et al., 1996; Mölle et al., 1997; White and Yee, 1997); and (3) that NE/CORT activity can modulate cognition (Roberts et al., 1976; Brozowski et al., 1979; Carli et al., 1983; McEwen and Sapolsky, 1995). However, the present study has shown that stress can modulate NE/CORT activity while concomitantly altering a cognitive measure of attention. Thus, the current findings integrate the findings of past biochemical and behavioral data, and can serve as a catalyst for new models of stress and attention.

One such model may involve the interaction between stress-induced NE release and neurons of the prefrontal cortex (PFC). It has been repeatedly shown that brainstem neurons, especially those in the LC, project to the PFC (Porriño and Goldman-Rakic, 1982; Lewis and Morrison, 1989; Berridge et al., 1993). It has also been shown that lesions to the right dorsal PFC induce deficits in attention (Woods and Knight, 1986; Wilkins et al., 1987; Chao and Knight, 1995) and that patients with attention-deficit hyperactivity disorder (ADHD) have a lower volume of PFC than normal individuals (Hynd et al., 1990). Based on the data found in the current experiment, it could be hypothesized that increasing LC activity and NE release modulates the PFC, producing a state of greater distractibility. This interpretation would be compatible with an evolutionary, func-

tional account of attention since organisms in the midst of a flight or fight response would need to widen their attentional focus. Thus, one would predict that the administration of NE agonists such as clonidine would disrupt performance on tasks which measure selective attention. However, research examining the effect of α_2 -NE agonists on cognition has shown that increasing NE levels actually improves PFC function, including measures of attention (Arnsten et al., 1988; Arnsten and Leslie, 1991; Arnsten and Contant, 1992; Cai et al., 1993). These disparate results could be explained by the fact that peripheral administration of α_2 -NE agonists work primarily on LC presynaptic autoreceptors. The binding of α_2 -NE agonists to autoreceptors serve to decrease the spontaneous firing rate of LC neurons, thus decreasing NE input to the PFC and other brain areas (Cooper et al., 1991). Hence, the improved performance on cognitive tasks when administered α_2 -NE agonists are actually due to a decrease in NE activity. Such a counterintuitive effect could account for the efficacy of stimulants such as methylphenidate in disorders such as ADHD, and would provide additional support that increased NE activity during stress deleteriously affects attention.

In order to have a complete model of how stress affects cognition, the dynamics of the glucocorticoid response must also be elucidated. In the present study, mean CORT levels did not rise after stress, indicating that either the stressor was too mild or the latency of CORT release was too great to be observed. However, since CORT concentrations after stress did correlate with NP scores, it is probable that glucocorticoids do play a role in relation to stress and cognition. Given the fact that CORT levels correlated with attentional inhibition only after stress, it is possible that there is a facilitatory effect of NE on CORT dynamics during the stress response. In other words, baseline CORT levels do not affect measures of attention at rest because there is no increase in NE release to augment CORT's effects. However, when CORT and NE are activated in parallel, levels of CORT can predict behavioral measures of attention. Evidence for this hypothesis comes from the fact that CORT

receptors are colocalized with catecholaminergic neurons, and that catecholamine activity is accentuated by CORT release and vice versa (Rothschild et al., 1985; Harfstrand et al., 1986; Deroche et al., 1993). Further research is necessary, however, to test this hypothesis directly, especially in relation to stress and information processing.

Several other questions stemming from the present experiment also require further elucidation. For example, while the reduced attentional inhibition after stress could be interpreted as a broadening of general attention, some of the classic work by Callaway and others has shown that stress actually narrows attention (for review see Venables, 1964). One possibility is that the present study tapped a specific subset of the process of attention: attentional inhibition. It has been shown that such processes are modulated in part by the septo-hippocampal system (Gray et al., 1991; Venables, 1992), while some of the tasks utilized by Callaway and others, for example the Stroop task, tap more anterior brain regions (e.g. anterior cingulate and frontal cortex) (Carter et al., 1995; Pardo et al., 1990; Casey et al., 1993). Thus, stress may have a differential effect on various subtypes of attentional processes, mediated by different neural networks.

Finally, while our results showed that mild stress can reduce selective attentional inhibition, previous work has demonstrated that similar stressors enhance memory function (McEwen and Sapolsky, 1995). It is possible that during stress, reduction of an organism's attentional inhibition actually has beneficial effects on memory processing, since additional environmental cues can be encoded during the salient event. Hence, the effects of CORT and NE on memory should also be examined. These and similar studies would further clarify the relationship between biochemical markers of stress, and the complex mechanisms of memory and attention.

Acknowledgements

We are grateful to Kelly Minor and Christine Hooker for their valuable input throughout the

project and to Aryeh Routtenberg, Kristen Andersen, Bill Revelle and David Fraser for their helpful comments. This work was supported by NARSAD, the Scottish Rite Schizophrenia Research program and NIMH.

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