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CBT-Efficacy and hCRH Induced Memory Enhancement

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## Introduction

An accumulation of data leaves little doubt that stress-related hormones—epinephrine and glucocorticoid, specifically—are vital components of memory retention and recall (McGaugh et al. 1996; Cahill et al. 1996; Cahill and McGaugh 1998; Kazui et al. 2000; O'Carroll et al. 1999; Roozendaal et al. 1996). Studies exploring the effects of epinephrine on memory retention found that infusion—directly into the amygdala in rat and peripherally via tablet in humans—of the  $\beta$ -adrenergic antagonist propranolol, which easily crosses the blood brain barrier, impairs memory retention of inhibitory avoidance in the rat and selectively impaired recall of emotionally salient images by human subjects (McGaugh et al. 1996; Stegeren et al. 1998). When glucocorticoid is administered to rats shortly after inhibitory response training, memory retention is enhanced (Cahill and McGaugh 1998). More specifically, amygdal glucocorticoid activity is strongly correlated with emotionally-affected memory (McGaugh et al. 1996; Cahill and McGaugh 1998). Posttraining infusion of glucocorticoid agonist into the basolateral nucleus of the amygdala (BL) in the rat enhances memory (Cahill and McGaugh 1998), and lesions of the BL block memory-enhancing effects of posttraining injections of dexamethasone, a synthetically produced form of glucocorticoid (McGaugh et al. 1996).

Abnormalities of sympathoadrenal functioning have been described in many depressed individuals, raising questions regarding a possible impact on their memory processes. In relation to this hypothesis, glucocorticoid release is normally attenuated in some clinically depressed patients pretreated with a low dose of dexamethasone, whereas some depressive patients show abnormal failure to suppress dexamethasone release (Holsboer 1999). Furthermore, it has been hypothesized that dysregulation of amygdal corticotropin-releasing-factor (CRH), which stimulates corticotropin (ACTH) production and, subsequently, glucocorticoid, may account for

“the sustained fear of personal unworthiness and dread of the future that are characteristic of melancholia” (Gold and Chrousos 1998 p. 26). It is unknown whether CRH alone, acting at CRH-1 receptors, or glucocorticoid effects on glucocorticoid-receptors (GR) in the amygdala is primarily responsible for this phenomenon.

To explore the relationship between stress-hormones and memory in depressed patients, a pilot study will assess memory impairment of clinically diagnosed depressive patients by using memory tasks comparable to those utilized in experiments by Cahill and McGaugh; in order to compare memory retention in patients with normal levels of glucocorticoid (a) to those with hypersecretion of glucocorticoid (b), injection of hCRH, which stimulates the production of glucocorticoid, will be administered prior to memory retention tasks. It is hypothesized that administration of hCRH to type (b) patients will enhance memory retention of emotionally salient content while type (a) patients, due to the hypothesized downregulation of GR (Holsboer 1999; Gold & Chrousos 1998), will show no significant memory enhancement relative to healthy controls. The findings of this study may suggest differential treatment plans for type (a) and (b) patients. Type (b) patients may benefit more from pharmaceutical treatment than type (a) patients.

Understanding physiological underpinnings of memory and attentional problems of depressed individuals can have important ramifications. Depressed individuals have been noted to have “disproportionate amount of time thinking gloomy or unpleasant thoughts” (Frank et al. 1999 p.461). Moreover, disturbed cognitive processes have long been implicated in sustaining depressive episodes (e.g., Beck). If the pilot study reveals a connection between variable expression of glucocorticoid in clinically depressed patients and memory retrieval and recall, then impaired memory—whether the impairment entails exaggerated enhancement or degradation—may indirectly reinforce pathological processes, i.e., excessive rumination and negative self-

evaluation. The hypothesized connection between stress-related hormone and memory impairment in depressed individuals, backed by research demonstrating such impairment (Rude et al. 1999), may provide one possible explanation for the efficacy of cognitive therapeutic techniques (which are known to target maladaptive interpretation and subsequent encoding of everyday life experience) for treating clinical depression (Frank et al. 1999 p.461-2; Jarrett et al. 1999; Brewin 1996 p. 45-7). If clinically depressed patients who hypersecrete glucocorticoid demonstrate variable performance on memory tasks, then the modulation of memory by way of amygdal glucocorticoid activity may provide an explanation for the relative success of cognitive therapy for depressive patients. The second study proposed below will assess whether clinically depressed individuals with normal levels of glucocorticoid (a) react differently to cognitive-behavioral therapy (CBT) than do depressed patients with elevated levels of glucocorticoid (b).

## Methods

### Subjects

A multifactorial 3 x 2 between subjects design will be used to assess the relationship between stress-hormones and memory in depressed patients of type (a) and (b) vs. healthy controls. To measure the relative circulation of glucocorticoid, blood samples will be drawn for each group member. Since glucocorticoid levels will vary between subjects, variations will be matched as close as possible for group members in each condition.

### Materials

Two films, each 20 minutes in length, depicting either emotionally arousing (E) content or relatively neutral (N) content will be presented following administration of hCRH or placebo. Film 1 (E) will present emotionally arousing clips that depict animal mutilations and violent crimes, whereas Film 2 (N) will depict relatively neutral clips (Cahill et al. 1996). Catheters will

be used to inject patients prior to screenings of both films. Catheters will contain either hCRH or nadol, a water soluble drug known to have no effect on memory retention (Stegeren 1998). Nadol will act as the placebo in this experiment.

### Procedure

Each group, 1-6, will have a N of 10. Groups 1-2 will be comprised of (a) clinically depressed patients with hypersecretion of glucocorticoid; groups 3-4 will be comprised of (b) clinically depressed patients with normal levels of glucocorticoid; and groups 5-6 will consist of healthy control subjects. Three independent variables—two subject variables (type a or b depressives) and one controlled variable, peripheral injection of hCRH—will be divided between each of the three groups. Placebo (nadol) or hCRH will be administered immediately preceding the screening of both films. Sequencing effects associated with viewing either the E or N film first may occur, so counterbalancing within each group will be necessary. Half of each group (5 subjects) will view the E film first and half will view the N film first. Below is an illustration of the design scheme for this study:

		<u>Pilot Study</u>	
		<b>+hCRH</b>	<b>-hCRH</b>
<b>Type A</b>		Film 1 (E) Film 2 (N)	Film 1 (E) Film 2 (N)
<b>Type B</b>		Film 1 (E) Film 2 (N)	Film 1 (E) Film 2 (N)
<b>Control</b>		Film 1 (E) Film 2 (N)	Film 1 (E) Film 2 (N)

Three weeks after the study, each member will be given a surprise call; they will be asked to recollect as many details as possible from both the E and N film.

## Subjects

This 2 x 2 between subjects study is designed to test the efficacy of cognitive-behavioral therapy (CBT) for type (a) and (b) depressives. Sessions 1-4 will all contain a N of 10 for both type (a) and (b) depressives.

## Procedure

Section (1) will receive hCRH immediately preceding CBT for 6 sessions over a 3 week span; section (2) will receive placebo pretreatment prior to CBT for 6 sessions over a 3 week span; section (3) will receive hCRH pretreatment prior to sham-therapy for 6 sessions over a 3 week span; and session (4) will receive neither pretreatment or therapy. Response to each of the three section's conditions will be measured by clinical assessment. Below is a diagram of the experimental design.

### Main Study

	<b>+hCRH</b>	<b>-hCRH</b>
<b>+CBT</b>	Section 1 Type A and B Response	Section 2 Type A and B Response
<b>-CBT</b>	Section 3 Type A and B Response	Section 4 Type A and B Response

### Anticipated Results

The exact dosage of CRH required to influence memory retention and recall in clinically depressed patients is unknown, and due to the potential downregulation of glucocorticoid receptors in clinically depressed patients (Gold & Chrousos 1999; Holsboer 1999), administration

of CRH may not have any bearing on glucocorticoid-memory interactions. CRH itself, however, may induce melancholic features associated with maladaptive memory processing, or the “sustained fear of personal unworthiness and dread of the future” (Gold & Chrousos 1999). With the assumption that glucocorticoid, released indirectly by CRH administration, will excite amygdala in clinically depressed patients, however, it can be assumed that session (1), or patients who received CBT but no pretreatment of dexamethasone, will perform comparably to participants in group (2), in which members received dexamethasone but not therapy. Session (3), on the other hand, should display enhanced recall of emotionally salient details in the E films relative to members in session (4), who should demonstrate globally reduced capacity to recall emotionally salient details. Session (4)'s performance should contrast sharply with session (5)'s performance. Main effects should be seen for both dexamethasone and cognitive therapy, with potentially significant interaction in session (2) between CBT and CRH administration.

### Discussion

The purpose of this study is to evaluate a hypothesized role of emotionally influenced memory in as an indirect means of reinforcing depressive symptomatology. Whether the action of the independent variable CRH is primary or secondary, whether CRH itself or the chain of chemical events precipitated by CRH is causing altered memory functioning, we can nonetheless predict, based on the literature cited in this paper, that stress-hormone induced emotionality will have significant impacts on memory retention and recall. And the difference in impact may account for the variable success of CBT. If CBT is less effective for depressed patients of type (a), then we may speculate that downregulation of GR in the prefrontal cortex, which has direct inhibitory projections to amygdala and hypothalamus (Gold & Chrousos 1999 p. 26), constrains the utility of acquired cognitive skills, or their effectiveness in combating depression. If, on the

other hand, CBT is equally as effective for both type (a) and (b) patients, regardless of the influence of CRH, then we may assume that the regulatory influence of prefrontal cortex overrides the degradation of other anatomical areas involved in depression. This outcome is highly unlikely given the profound, exclusive affects of amygdal and hypothalamic dysregulation on behavior in rats.

The main effects of CRH on CBT are of utmost importance. If CRH enhances the efficacy of CBT in depressed patients of type (b), then short-term administration of CRH can be assumed to interact with the encoding of memories during the therapeutic session. Either the memories during therapy are given privileged encoding as a result of artificially induced (stress-hormone related) emotional arousal, or CRH itself is enhancing the recall of therapeutic memories. This outcome (enhanced efficacy of CBT for depressed patients of type [b]) may prompt a shift in strategy for treating depressive patients: rather than using pharmacotherapy, as it is traditionally conceived, to treat depression, it may be more cost-effective to treat patients with some form of memory-enhancing agent in combination with CBT. Several outcomes are possible in this design, yet most of them would be unexpected based on *a priori* knowledge of clinical depression and stress-hormone levels. All main effects for CRH would require further studies.

Main effects for CBT, unless paired with CRH, are not under question in this study; however, if CBT is less successful for type (a) depressives (clinically depressed individuals with hypocortisolism) compared to type (b) depressives (depressed individuals with normal levels of cortisol), then dysregulation of the HPA axis and accompanying side effects (influences on other anatomical regions, i.e., amygdala, hippocampus, and prefrontal cortex) would be hypothetically involved in the capacity for CBT patients to encode or retrieve memories acquired from therapeutic sessions.

Regardless of the outcomes of any of the conditions in the main experiment, we can predict four possible outcomes: (i) hypercortisolism and resulting downregulation of GR is the primary, physiological correlate of memory dysfunction; (ii) CRH-induced chemical changes, which include intracellular effects, secondary glucocorticoid effects (interaction with hippocampus, amygdala, accumbens, and prefrontal cortex); (iii) primary CRH activity in hippocampus, amygdala, accumbens, and prefrontal cortex; or (iv), the most likely explanation, the combination of activity outlined in (i-iii). The latter outcome (iv) is supported by speculations drawn by Gold and Chrousos:

The reciprocal connectivity of the circuitry shown in Figure 4 suggests that a similar phenotype can be generated by primary defects in either the prefrontal cortex, amygdala, hippocampus, or hypothalamus. For example, 1) primary hypoactivity of the medial prefrontal cortex would lead to disinhibition of the amygdala and HPA axis; 2) an activated amygdala would further intensify HPA axis function; 3) the amygdala and hypothalamic CRH systems would each activate brainstem arousal and autonomic centers; and 4) chronic hypercortisolism would lead to progressive damage of the hippocampus and accentuation of the amygdala fear system. Alternatively, primary hyperactivity of the amygdala could simultaneously activate dysphorically charged emotional memories, the HPA axis, and brainstem autonomic arousal and autonomic centers, leading to a similar phenotype (p. 26).

Based on Gold and Chrousos' speculations (1-4 above) and contingencies i-iv of my experimental design, it is clear that *dissociation of function* is a necessary precondition for any theoretical model related to stress-hormone and memory. Ideally, chemical antagonists that selectively block cortisol could be used to test its functional differences vis-à-vis epinephrine. Potential confounds may exist, also: if depressive patients of type (a) have downregulated mesolimbic reward systems, then emotionally salient life-experiences may be interpreted as neutral events, which in turn prevents any experiential/interpersonal means of producing endogenous neural agents that combat dysregulation of the HPA axis. In other words, dopamine affects on learning and memory may prove to be significant.

Studies by Fuster (2000), Schoenbaum et al. (1998), and Bechara et al. (1999) demonstrate the profound interchange between prefrontal cortex activity and emotionally influenced memory. Short-term memory encoding of emotionally salient events has been correlated with prefrontal cortex activity, which has been hypothesized to play a primary role in subjectively experienced emotional arousal (LeDoux 175-7 2000). Since the prefrontal cortex is hypothetically involved in higher-order, meta-cognitive processing, which entails accessing and memory networks stored throughout the brain, all of these studies allude to the interaction between the environment and the organism: if conscious experience of feeling-states interacts with implicit and explicit memory systems, then everything we encounter will be affected by (a) pre-immanent, emotionally-graded memories (experience) and (b) the our conscious appraisal of new experience based on negative or positive emotional feedback. If dysregulation of the HPA axis involves alterations of (a) and (b), then we must recognize the profound affect new memory storage may have on reinforcing depressive symptoms. Future studies, therefore, must concentrate on environmental factors in relation to physiology—whether physiology is altered by the environment or the environment is altered (in relation to memory) by physiology. Thus, my “personal agenda” is motivated by the political movement in psychology to approach new problems from an interdisciplinary perspective—a mutually reciprocal combination of brain physiology and social psychology.

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