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Opioid blockade improves human recognition memory following physiological arousal

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Abstract

Rationale: States of heightened emotion and arousal, such as those that may occur during crimes or traumatic accidents, can impair human memory. Animal models suggest that such memory alterations may be mediated by opioid neuropeptides. In some experimental paradigms, opioid blockade reverses memory impairments related to arousal. **Objectives:** The present study evaluated the hypothesis that, under conditions of heightened arousal, opioid blockade would enhance memory in human subjects. **Methods:** Memory for story information was evaluated among subjects randomized to one of four study groups (two orthogonal study conditions): (1) no arousal + no opioid blockade, (2) no arousal + opioid blockade, (3) arousal + no opioid blockade, and (4) arousal + opioid blockade. Both free recall and recognition memory were assessed. Opioid receptor blockade was achieved using a single oral dose of naltrexone. **Results:** With heightened arousal, subjects receiving naltrexone performed better than those receiving placebo on tests of total and incidental recognition memory. In contrast, with emotionally neutral stimuli, naltrexone subjects performed worse than placebo subjects. **Conclusions:** These findings demonstrate that opioid peptides mediate alterations in specific aspects of human memory during heightened emotional states, and help to explain why memories may be selectively deficient under conditions of stress.

Keywords: Opioid blockade; Stress; Memory

1. Introduction

The implications of the fallibility of human memory have attracted considerable research to this area. Previous studies have demonstrated the ease with which memory can be manipulated, such that an observer's recall may in fact contradict detailed recordings of actual events (Christianson, 1992; Loftus et al., 1978; McGaugh, 1972). An individual's emotional and cognitive appraisal of what is to be remembered produces physiological and neural changes that may contribute to the subsequent distortion of memory for those events (Boff et al., 1986; Heuer and Reisberg, 1990; Loftus and Burns, 1982; Schmitt, 1970).

A substantial body of research describes the involvement of opioid neurotransmitter systems in emotion, arousal, learning, and memory. Messenger RNAs for the endogenous opioids, dynorphin and enkephalin, are constitutively expressed at high levels in the limbic system, a brain system central to emotion and memory (Hurd, 1996). Endogenous opioid neuropeptides are released during states of physiological arousal and stress, and have been associated with memory deficits (Gallagher, 1982; Hernandez et al., 1997; Izquierdo, 1979; McGaugh and Herz, 1972; Squire and Davis, 1981). Furthermore, it has been shown that exogenously administered opioids alter memory both in animals and humans (Braida et al., 1994; Hanks et al., 1995). Even classical conditioning, the simplest form of learning, is impaired by the administration of opioid agonists, and improves with opioid antagonist treatment (Collier et al., 1981; Gallagher, 1992; Izquierdo, 1979).

Opioid peptides may impair memory through several different mechanisms. For example, endogenous opioids could downregulate affect and motivation, thereby reducing attention and diminishing the depth to which stimuli are encoded (Gallagher, 1992; Squire and Davis, 1981). Such effects of opioids on attention could be mediated by

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changes in acetylcholine release (Collier et al., 1981). Alternatively, opioids might impair memory by disrupting memory consolidation (Cestari and Castellano, 1997) or retrieval processes (Ilyutchenok and Dubrovina, 1995).

Opioid systems interact with dopaminergic, β-adrenergic, and endogenous cannabinoid systems in their mediation of emotional states, arousal and memory (Cahill, 1998; Cestari and Castellano, 1997; Zanatta et al., 1997). Of particular importance are interactions between the opioid and adrenergic systems in the amygdala. Limbic opioid systems modulate β-adrenoceptors in the basolateral nucleus of the amygdala, affecting arousal and memory (Cahill, 1998; Cahill et al., 1994; Ferry and McGaugh, 1999; Introini-Collison et al., 1995, 1996; McGaugh et al., 1996). In one study, administration of the sympathomimetic β-2 adrenergic agonist, clenbuterol, into the amygdala of rats after training attenuated the retention-impairing effects of β-endorphin in an inhibitory avoidance task (Introini-Collison et al., 1995).

These interactions between systems modulating affect and memory have been the focus of a great deal of research. Both rodent and human research strongly suggest that enhanced memory during affective arousal results from activation of β-adrenergic systems before, during, and after an emotionally arousing or stressful experience (Cahill, 1998; Ferry et al., 1999; Introini-Collison et al., 1996; McGaugh and Cahill, 1997). During states of emotional arousal, the neuromodulatory function of the amygdala has been found to impact memory consolidation (Ferry et al., 1999; Liang et al., 1996; Roozendaal et al., 1999; Wilensky et al., 2000). In animals, lesions to the amygdala and administration of β-adrenergic antagonists ("β-blockers") attenuate the beneficial effects of emotional arousal on memory (McGaugh et al., 1996; Wilensky et al., 2000).

Previous studies have demonstrated that β-adrenergic blockade in humans using propranolol resulted in impaired memory for an emotionally charged story but did not affect memory for a neutral story, supporting the hypothesis that enhanced memory associated with emotional experiences involves activation of the β-adrenergic system (Cahill et al., 1994). We sought to extend the findings of this study by examining the effects of opioid systems on memory using a similar paradigm. We evaluated memory in an experimental task among volunteers given naltrexone, an opioid antagonist, or placebo. Because previous research indicated that opioid peptides may influence memory by altering arousal or motivation, we manipulated subjects' state of arousal by contrasting two different versions of a stimulus presentation that took the form of a story. In one version, the story line was punctuated by a grave personal injury to a central character, to elicit subjects' emotional concern and to heighten attention. In the contrasting version, nearly identical stimulus material was presented, except that the personal injury segment was replaced by a mundane, emotionally neutral event. The effect of naltrexone on memory for stimulus material in the two conditions was assessed.

To determine whether opioid systems principally acted on memory at "early" or "middle" stages of processing (registration, encoding, and consolidation) or at a very "late" stage (retrieval), two different formats were used to test subjects' memory for the story material: free recall and recognition memory. We examined the effects of opioid antagonism on memory for various stimulus dimensions, including elements central to the story line (thematic), elements that could be changed without altering the story's basic premise (incidental), and elements that varied according to spatial location in the stimulus array (central and peripheral).

2. Methods

2.1. Subjects

Fifty-two participants, an equal number of males and females, were recruited from the greater San Diego area, an educationally and culturally diverse community. Potential subjects ranged in age from 18 to 60 years. They were screened by telephone prior to testing to determine if they met inclusion criteria. Although participation was voluntary, participants were paid US $ 15.00 for their time.

Subjects were excluded from the study if they: (a) had witnessed or been the victim of any psychologically traumatic event; (b) had a medical history of significant hypertension, heart disease, renal disease, liver disease, mental illness, or seizure disorder; (c) were currently taking narcotic medications or had a history of narcotic addiction or recreational use of narcotics within three months of the study period; and (d) were currently pregnant or lactating.

Subjects were treated in accordance with guidelines established by the Institutional Review Board at the California School of Professional Psychology, San Diego, as well as with the Ethical Principals in the Conduct of Research with Human Participants (APA, 1984). They were informed of the nature of the study and given a clear explanation of the experimental procedures.

2.1.1. Design

The experiment was conducted as a randomized, double-blind, parallel-groups, placebo-controlled study. Subjects were randomly assigned to one of two drug treatment conditions (naltrexone vs. placebo), and to one of two story conditions (arousal vs. neutral). Participant gender was counterbalanced across the two experimental story conditions.

2.1.2. Materials

The experimental stimuli consisted of a series of 10 projected 35-mm slides, presented in fixed order, accom-

panied by narration on a prerecorded audio tape. The entire presentation was timed by a Commodore computer and had a duration of 60 s. One of two story versions was presented, comprising the two experimental conditions: arousal versus neutral. For purposes of analysis, the slide presentation was divided into three phases: (1) an introduction, (2) an experimental phase (arousal vs. neutral), and (3) a conclusion. The slides and narration were derived, with slight variation, from those used previously by Heuer and Resiberg (1990) and Cahill and McGaugh (1995). In the arousal story, the subjects were told that the main character had been critically injured, while, in the neutral story, they were told that a medical team was practicing a mock disaster drill. The 10 slides were visually identical in each condition with the exception of slide #7 of the arousal story, which graphically depicted the traumatically amputated and then surgically reattached legs of the story's main character. In the neutral story, slide #7 depicted a medical team around an empty operating table.

2.1.3. Physiologic measures

Heart rate was monitored continuously during the experiment by a photoplethysmograph (PPG) attached to the thumb of the left hand. These data were digitized by a transducer, the J&J I-330, for subsequent analyses. Heart rates were sampled every 6 s over 1.5 min (i.e., for 30 s prior to, and during, the 60-s stimulus presentation). The lowest heart rate (LHR) recorded during each time period of interest was taken as an index of physiological arousal. LHR was recorded at baseline (prior to stimulus presentation) and during each of the three sequential story phases.

2.1.4. Study drug

Naltrexone has been shown to be an effective opioid antagonist when administered at 50 mg orally (O'Connor et al., 1997). The average time to peak blood concentration is 1 h, and the mean elimination half-life value is 3.9 h (PDR, 1992). DuPont-Merck Pharmaceuticals provided naltrexone (as a single white tablet) and a matching placebo. For each dose of study drug, a code was available to be broken in case of suspected adverse drug reaction. Approval for administration of the study drug in this experimental setting was obtained from the United States Food and Drug Administration.

2.1.5. Self report measures

The Profile of Mood States (McNair et al., 1992) is a paper-and-pencil, self-report questionnaire consisting of 65 items addressing current mood state. Responses are scored on a five-point Likert-type scale, indicating the subject's level of agreement with a statement concerning his or her mood, e.g., "During the past week, I have been feeling *on edge*." Only the Tension scale of the POMS (POMS-T), comprised of nine items dealing with subjective anxiety and tension, was used in the present study.

2.1.6. Memory tests

Two memory test formats were used. The first was a semistructured free recall test comprised of five questions that were identical for the two story versions. Information from four general categories was elicited: color, people, written numbers, and proper names. Subjects were asked to provide details central to the story line, as well as incidental information not clearly pertinent to the story events.

The second test instrument was a recognition memory test, adapted from a previous study (Cahill and McGaugh, 1995), with minor changes to accommodate revisions to the original slide presentation as noted previously. The recognition test consisted of 67 questions, which were answered using a forced-choice response format.

To facilitate the analysis of recognition memory test performance, each of the to-be-remembered story elements was classified by type. The classification system was devised by consensus among three of the study investigators, and was operationally titled the Salience Classification System (SCS). Combining the terminology of other memory researchers, the SCS classified individual story elements as (1) either thematic or incidental in relation to the story line and (2) either central or peripheral in spatial location. "Thematic" material represented elements that could not be changed or deleted without substantially altering the story's meaning (Burke et al., 1992). "Incidental" items were defined as those not satisfying the criteria for thematic elements. "Central" story elements were those located spatially outside the middle diameter of the slide. Four categories of information were thus designated: central-thematic, central-incidental, peripheral-thematic, and peripheral-incidental. For those stimulus elements which spanned both the central and peripheral parts of the picture, or for those that were heard, rather than seen, only the thematic versus incidental classification was used.

Sixty-one of the 67 recognition test items were identical between the two experimental stimulus conditions. The remaining six questions referred to the details of slide #7, and therefore differed between the arousal and neutral story groups. These six questions were equally distributed with respect to their SCS categorization.

2.2. Procedures

Fig. 1 schematically depicts the sequence of study procedures. Participants were tested individually by a single examiner who was blinded to drug condition. By way of orientation, subjects were instructed that the study was designed to measure physical reactions to psychological stress. The subsequent memory assessments were not mentioned. Baseline heart rate and respiratory rate were taken, and electrodermal responses (EDR) were recorded for 90 s. If vital parameters were normal and informed consent was given, study drug was administered by a registered nurse. Subjects were then monitored in a quiet waiting area where the POMS-T was administered. Forty minutes after receiving

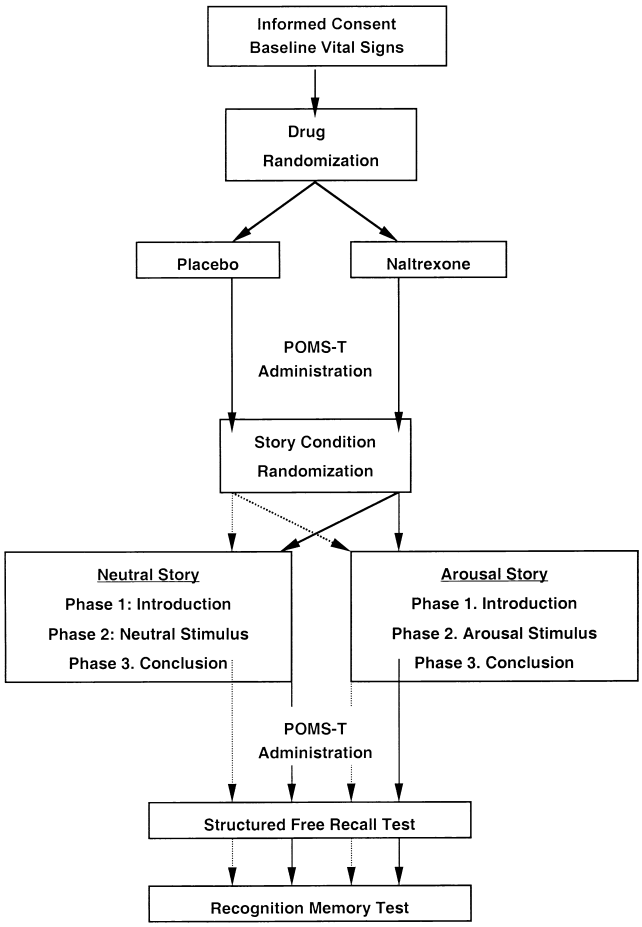

Fig. 1. Schematic of the study procedures (see text for detail).

study drug, they were brought into a darkened, temperature- and noise-controlled room, and were seated comfortably in front of a stimulus screen at a distance of 54 in. The left hand was secured on a pillow. Before stimulus presentation, standardized verbal instructions were given which included the phrase "watch and listen carefully."

Stimulus presentation began 45 min after administration of the study drug. Slides were rear-projected onto a 22 × 15 in. white screen. Each slide was shown for 5 s with an inter-stimulus interval (ISI) of 1 s. Heart rate was sampled digitally once per second during each slide presentation and ISI. Immediately after the presentation, the subjects were taken to a quiet testing area and the POMS-T was readministered. When finished, they were asked to remain seated without any verbal interaction. Fifteen minutes after the slide presentation (1 h after the ingestion of the study drug), the two "surprise" memory tests were given. Participants were simply told to do their "best." Following testing, subjects were debriefed extensively.

2.3. Statistical analyses

Separate analyses of variance (ANOVAs) were performed to evaluate group differences for memory test performance, self-report measures, and heart rate or heart rate changes. For total recognition and free recall memory test performance, and for the POMS-T self-report questionnaire, raw scores (number of questions correctly recalled and tension scale total score, respectively) are reported. For recognition subcategories (thematic-incidental and central peripheral), percent of items correctly recalled was reported to facilitate comparisons between the categories. Heart rates were analyzed both as per subject means for a specific time interval (e.g., phase 1 and story introduction), and as LHR during each interval. The findings using these two methods did not differ, and only the LHR data are reported here. Independent variables included in the ANOVAs were as follows: drug group (naltrexone vs. placebo), story condition (arousal vs. neutral), and stimulus phase (introduction, experimental stimulus and conclusion).

3. Results

Fifty-two subjects completed the study. Of these, 26 were randomized to naltrexone and 26 to placebo. Subjects in the naltrexone and placebo groups did not differ with respect to age or education ($P > .5$). Twenty-six subjects were exposed to the arousal story and 26 to the neutral story.

3.1. Physiological arousal

In a 2 × 2 (Drug × Story condition) ANOVA, baseline (pretest) LHR were similar across subjects [mean 85.7 (S.D. = 10.0) beats per minute; range 60–100]. Similarly, mean LHR for the three groups did not differ during story phase 1 (mean 70.6). A three-way ANOVA (Drug × Phase × Story condition) for LHR demonstrated a significant interaction between phase and story condition

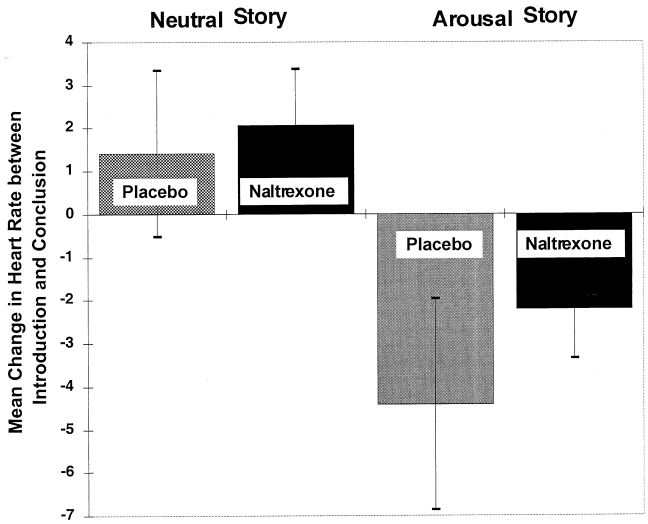

Fig. 2. Mean change in heart rate for each group from the introduction to the conclusion phase.

($F=6.48$, $P=.002$). Mean LHR decreased from the story introduction phase to the conclusion phase for subjects in the arousal condition, but not for those in the neutral condition (-3.3 vs. $+1.7$ beats/min, respectively). Fig. 2 shows mean changes in heart rate for each group from the introduction to the conclusion phase. None of the main effects or remaining interaction terms was significant.

3.2. Mood states

Total scores on the POMS-T scale were recorded for each subject at two time points: (1) at baseline and (2) immediately after the slide presentation (before memory testing). In a three-way ANOVA (Drug × Time × Story condition), there was a significant main effect of time ($F=7.96$, $P<.007$). Hence, across all subjects, the mean POMS-T score decreased from 9.4 (±6.95) at baseline to 7.4 (±5.45) following the slide presentation. The remaining main effect and the interaction terms were not significant.

3.3. Free recall

Data from the free recall testing format were analyzed separately. In a 2 × 2 (Drug × Story) ANOVA, the overall model was significant [$F(3,48)=3.9$, $P=.01$], as was the drug main effect [$F(3,48)=8.44$, $P=.006$]. Subjects receiving naltrexone performed worse than those receiving placebo [mean number of items correctly recalled, 4.0 (1.7) vs. 5.4 (1.7), respectively; a 26% difference]. The story condition main effect was not significant. The interaction term showed a trend towards significance ($F=3.15$, $P=.082$), and, in post-hoc analyses, the poor performance of naltrexone-neutral subjects accounted disproportionately for the drug main effect [naltrexone-neutral vs. placebo-neutral, 3.7 (1.9) vs. 5.9 (2.0), $P=.008$; naltrexone-arousal vs. placebo-arousal, 4.4 (1.4) vs. 4.9 (1.4), $P=.34$].

3.4. Recognition memory

For the entire subject sample, the mean number of items answered correctly on the recognition memory test was 39.6 (S.D. = 8.1, range 18–53) of the 67 total items. In a 2 × 2 (Drug × Story) ANOVA, both the overall model ($F=3.38$, $P=.026$) and the interaction term ($F=8.21$, $P=.006$) were significant. In the neutral story condition, performance was adversely affected by naltrexone compared to placebo [mean score 34.3 (±4.85) vs. 43.0 (±6.25), $P=.003$], while in the arousal story condition naltrexone benefited performance [42.2 (±10.3) vs. 38.7 (±7.7), $P<.006$]. The ANOVA main effects were not significant.

Separate ANOVAs were then performed for thematic and incidental recognition memory, respectively. The pattern of results for these two categories of stimulus information differed. For thematic story material, the overall ANOVA was significant ($F=5.37$, $P<.003$), and a significant main effect of story condition was observed ($F=12.4$, $P<.001$). Subjects shown the arousal story performed better than those exposed to the neutral story [mean percent correct 85 (±16) vs. 65 (±13), $P=.027$]. Neither the drug main effect, nor the Drug × Story interaction, was significant. For incidental (nonthematic) story material, the overall ANOVA was significant ($F=6.37$, $P<.001$). This was due to a significant interaction of Drug × Story condition ($F=9.75$, $P<.003$); however, neither of the main effects was significant. Thus, for the neutral story, subjects receiving naltrexone performed worse than those receiving the placebo [mean percent correct 31 (±16) vs. 61 (±14)], while in contrast, for the arousal story naltrexone benefited performance [78 (±13) vs. 43 (±16), a 35% improvement]. Fig. 3 shows the Drug × Story interaction for incidental recognition memory.

Separate analyses for central and peripheral incidental recognition produced similar patterns of results. For central-incidental stimulus material, there was a significant Drug × Story interaction ($F=6.17$, $P=.017$), and a trend towards a drug main effect ($F=3.39$, $P=.072$). The naltrexone-neutral group showed poorer performance than the placebo-neutral group (mean percent correct, 45 vs. 60); while in contrast the naltrexone-arousal group showed slightly better performance than the placebo-arousal group (50 vs. 48). Similarly, for peripheral-incidental information the Drug × Story interaction was significant [$F=7.79$, $P<.01$]; the naltrexone-neutral group remembered less than the placebo-neutral group (31 vs. 50), while the naltrexone-arousal group remembered more than the placebo-arousal group (54 vs. 43).

3.5. Gender effects

Potential gender differences were analyzed for all groups and conditions (e.g., LHR, stress group, drug group, slide variations, etc.) and no significant differences were found.

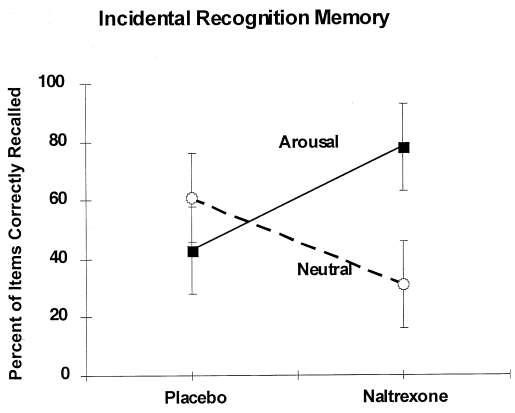

Fig. 3. Interaction between drug and story condition for incidental recognition memory. In the arousal condition (squares), naltrexone administration resulted in improved memory compared to placebo, while in the neutral condition (circles), naltrexone was associated with poorer memory.

3.6. Safety and tolerability

One of the study volunteers complained of light-headedness and palpitations after receiving study drug. This subject underwent an examination at a medical clinic and did not complete the study. On follow-up, she reported having recovered without incident. Upon breaking of the study blind, she was found to have taken active drug (naltrexone). The remaining subjects completed the study without reported adverse effects.

4. Discussion

The principal finding of this study was that subjects receiving an opioid receptor antagonist performed better in a specific aspect of memory, recognition of incidental (nonthematic) material from a presented story, than did subjects receiving placebo. This improvement in memory was found only under experimentally induced conditions of physiological arousal. Increased arousal, as evidenced by decreases in heart rate (the so-called "orienting response"), was elicited by presenting a story in which a central character suffered a grave personal injury. In contrast to incidental material, memory for thematic material was better with the arousal story compared to the neutral story, and was not affected by opioid receptor antagonism. When a story with emotionally neutral content was presented, opioid antagonism led to impairments in memory performance. Thus, in the arousal condition, naltrexone improved recognition memory for incidental elements at no expense to memory for thematic material. As a result, naltrexone improved overall recognition memory. By inference, the "normal" operation of opioid-peptide-based neural mechanisms during arousal was deleterious to memory for nonthematic story material. These findings are consistent with previous studies showing that brain opioid systems can modify memory and learning processes, and suggest some specific mechanisms by which these effects may be mediated.

The Yerkes–Dodson model (Yerkes and Dodson, 1908) provides a useful heuristic to explain the findings of the present study. The adapted model, illustrated in Fig. 4, describes the relationship between arousal and memory as an inverted, U-shaped curve. When levels of arousal are moderately increased, memory performance is enhanced; however, when excessive arousal occurs, memory performance is impaired. We hypothesize that naltrexone shifts the arousal-performance curve to the right, resulting in improved performance under conditions of arousal, and causing deleterious effects under neutral conditions.

The present study compared free recall and recognition memory performance during periods of low (neutral story condition) and increased (arousal story condition) arousal. Overall, free recall performance was poor for subjects in both story conditions, and it was particularly poor for those receiving naltrexone. The negative effect on free recall performance was somewhat larger for the neutral story as compared to the arousal story. The free recall format required subjects to generate active retrieval strategies for accessing stored information. Naltrexone may have deleteriously affected the generation of these retrieval strategies, resulting in poor performance during free recall.

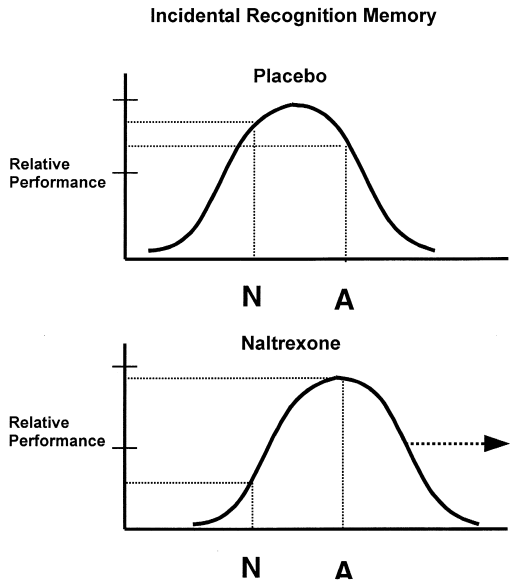

Fig. 4. The Yerkes Dodson effect as applied to the present experiment. The model postules that incidental recognition performance is related to arousal by an inverted U-shaped function, where moderate levels of arousal (N) benefit performance, while further increases in arousal (A) impair performance. Naltrexone shifts the arousal-performance function to the right, resulting in decreased performance in the neutral condition, but improved performance in the arousal condition.

By contrast, using the recognition memory testing format made lesser demands on subjects' retrieval processes. Accordingly, the deleterious effects of naltrexone on retrieval were not evident. In fact, naltrexone appeared to benefit recognition memory, specifically when arousal was heightened. Arousal may have lead to an increase in stimulus registration, encoding, or consolidation that was further unmasked by opioid blockade in subjects that received naltrexone.

Similar to previous studies (Heuer and Reisberg, 1990), we found that memory for thematic details improved when an emotionally compelling story was presented, as compared to a neutral story. Significant decreases in heart rate coincided with the climax of the arousal story, reflecting changes in subjects' physiological and emotional state. It is noteworthy that the improved recall of thematic story material did not result in a reciprocal decline in memory for incidental elements. A possible explanation for the improved thematic memory with arousal is a general heightening of attention. This "orienting response" is considered to be a gating phenomenon that permits the

evaluation of a stimulus with respect to salience, importance or meaning (Walsh, 1978). The orienting response may be mediated by the reticular activating system, possibly through adrenergic mechanisms (Venables and Christie, 1975). Attentional enhancement by the orienting response would be expected to facilitate stimulus registration and encoding, a view that is supported by the differences in free recall and recognition testing in our study. Consistent with our findings, animal studies have demonstrated that opioid agonists diminish attention, while antagonists enhance the orienting response (Gallagher, 1982; Izquierdo, 1979).

A possible explanation for subjects' better memory for thematic material from the arousal, as compared to the neutral story is that the neutral test items were more difficult. This explanation seems unlikely, however, since 61 of the 67 test items (91%) were identical between the two story conditions,. The remaining six test items (those pertaining to slide #7) were as similar as possible in content and complexity for the two story versions. In a separate analysis (data not reported), there were no differences in performance between the arousal and neutral groups for these six test items.

Nonspecific mechanisms such as anxiety or distractibility might have accounted for some of the adverse effects of naltrexone on memory performance. However, the administration of naltrexone itself had no effect on physiological arousal or subjective tension as measured by the heart rate and self-report (POMS), respectively. Both the naltrexone and placebo groups showed uniform decreases in self-reported anxiety that were clearly related to completion of the experimental phase (i.e., they occurred after the stimulus presentation was completed). Nonspecific naltrexone effects, such as those due to anxiety, might be expected to produce decrements in scattered areas of test performance, rather than the specific patterns of improvements and decrements that we observed.

The beneficial effects of naltrexone in the arousal condition were specific for *incidental* recognition memory. Recall of such "incidental" details is important in many real-life circumstances, where these details may distinguish the perpetrators of a crime, for example.

Because opioid antagonists such as naltrexone are used in the treatment of substance use disorders, our study's findings may have specific clinical implications. We found that naltrexone administration in subjects exposed to a neutral story resulted in consistent decrements in memory performance. Substance abusers in treatment undergo cognitive therapies designed to modify their behavior patterns, placing a substantial burden on their ability to learn new information. Since naltrexone-induced memory impairment would be expected to interfere with such cognitive treatment modalities under normal (neutral) arousal conditions, our findings may argue against the clinical use of opioid antagonists in the treatment of substance use disorders.

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