Pharmacology Biochemistry & Behavior, Vol. 11, pp. 521–527. Printed in the U.S.A.

Methadone Depression of Visual Signal Detection Performance[1]

S. ROTHENBERG, E. A. PECK,[2] S. SCHOTTENFELD, G. E. BETLEY, AND J. L. ALTMAN[3]

Harvard-Boston University Center for Biobehavioral Studies in the Addictions, Harvard Medical School, Alcohol and Drug Abuse Research Center, McLean Hospital, Belmont, MA 02178

Received 5 July 1979

ROTHENBERG, S., E. A. PECK, S. SCHOTTENFELD, C. E. BETLEY AND J. L. ALTMAN. *Methadone depression of visual signal detection performance.* PHARMAC. BIOCHEM. BEHAV. 11(5) 521–527, 1979.—In order to determine the origin of a previously reported slowing of simple visual reaction time in subjects receiving single doses of oral methadone, three well-trained subjects performed a modified double flash detection task several times after single doses of 5 mg and 10 mg of oral methadone and a placebo. A Theory of Signal Detectability analysis allowed for a clear distinction between drug-induced changes in visual sensitivity and changes in response bias. It was found that methadone reduced visual sensitivity. The peak depression in detection as well as the duration of the depressed performance were dose-related. Depression in performance paralleled the subjective effect of the drug in each subject. Averaged visual evoked potentials showed significant changes at peak drug effect to the onset of each of the pair of stimuli. It was concluded that methadone depresses visual function by acting on the visual parts of the central nervous system. The retina, midbrain and thalamic visual nuclei were discussed as possible sites of action of methadone.

Opioids Methadone Visual sensitivity Visual evoked potentials Theory of signal detectability Humans

INFORMATION transmitted through the sense organs usually results in the initiation and determination of behavior. Thus, an accounting of drug effects on behavior would not be complete without a description of drug effects on sensory function.

Addicts maintained on methadone had faster simple visual reaction times than non-addicts [7]. A follow-up study controlled for motivation and attention in the two groups and replicated the superior addict performance [20]. The follow-up study also demonstrated that up to 10 mg of oral methadone significantly lengthened visual reaction times among non-addict controls, while additional methadone had no effect on addict performance. The investigators suggested that chronic use of methadone was associated with increased visual sensitivity, while acute use produced decreased visual sensitivity.

The present study tests for reduction of visual sensitivity with single doses of methadone. We have chosen a psychophysical procedure for this study since such methods provide a precise description of input-output functions of organisms. In addition to providing a test for the hypothesis that single-dose methadone decreases visual function, a psychophysical investigation of drug effect on sensory mechanism is an important starting point for subsequent investigations of drug action on more complex behavior.

The experiment was devised and carried out within the framework of the Theory of Signal Detectability (TSD). TSD, originally developed by communication engineers to describe the characteristics of ideal detectors of electromagnetic signals in noise, was quickly recognized by psychologists as offering a possible solution to problems of response bias in classical psychophysics [8,22].

If certain assumptions are met (e.g., knowledge of the form of the underlying distribution of the subject's signal space, equal variance of the two distributions of signal space and noise space), a TSD analysis of a psychophysical experiment yields two independent measures of performance. The subject's ability to receive the physical stimulus effectively, transform some aspect of it and map that transformation on to his signal space is characterized by the parameter d'. On the other hand, the measure describing how the subject evaluates the information that reaches him is termed β. Just as both external and internal manipulation can affect d' (a discrimination may be made more difficult by decreasing the physical difference between the two sorts of trials *or* by decreasing the sensitivity of the receptor organ), β can also be affected externally and internally (the subject's expectation of what the next trial may be can be changed by altering the *a priori* probability of presentation of the two stimulus types as well as by giving a drug which affects judgments).

The advantage of TSD over the classical psychophysical approaches is that alteration in the subject's performance due to stimulus change or change in the subject himself can

[1]This research was supported by NIDA Grant no. DA 01226.

[2]Present address: Department of Rehabilitation Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA.
[3]Present address: Narcotic Treatment Centre, 1755 W. Broadway, Vancouver, British Columbia, Canada V6J 4S5.

be analyzed by the two measures, d' and β. We may determine, to the extent that we meet the assumptions of the theory, if a drug-induced change in performance is due to reduction of sensory capacity or a shift in decision-making processes. We report here the effects of 5 mg and 10 mg of methadone and of a placebo on such performance, in the visual system.

METHOD

Subjects were between 21 and 40 years, had no prior experience with opioids, little or no incidental drug use and adequate visual acuity. Informed consents were obtained. They were paid for their service based upon their performance. The method of obtaining their earnings is described below.

Task

A double flash discrimination test was adapted from a well studied paradigm [15]. All stimuli were presented on a modified Gerbrands four-field tachistoscope. Subjects fixated on a small dot in the middle of a dimly illuminated (less than 0.3 cd/m^2) rectangular field through an artificial pupil, the field subtending 6° horizontally and 4° vertically. The artificial pupil served to limit light entering the eye for all subject pupil diameters larger than 1.6 mm. At intervals of 3.4 sec the dimly illuminated fixation field was interrupted by one of two stimuli. On any run of 100 trials, half the trials consisted of two bright flashes (4.5 cd/m^2) replacing the fixation field. Each flash was 300 msec long and each was separated from the other by a dimmer five msec gap. The luminance of the dimmer gap could be adjusted to provide any degree of detection difficulty. The subjective impression of the double flash trials was a bright flash of light with a flicker in it. In the remaining half of the trials a single flash of light 600 msec long replaced the fixation field. The subjects were asked to respond to the double flash trials by pressing a button. Stimulus sequencing, data collection, data analysis and display were automatically controlled by a programmable laboratory computer operating system [21].

Subjects were tested in an IAC 1203 A soundproofed, shielded room. Ambient light levels were held approximately equal to the level of the fixation field. Testing sessions were preceded by a 15 min adaptation period to the ambient level.

Data collection was divided into three parts: training, Receiver Operating Characteristic (ROC) determination, and drug testing. Each training session was about two hours long, consisting of several runs of 100 trials, each lasting six minutes, each run followed by a 5-min rest period. Subjects participated for as many as three such sessions per day, each session followed by a two-hour break. Within all sessions, subjects were notified of the impending start of a run by the onset of a moderate level of white noise (approximately 50 dB above threshold) delivered through Koss Pro 4AA earphones. The white noise remained on until the end of the run, both to mask subject generated sounds within the room and to signal the end of the run.

Training

Early training sessions were devoted to fixing the luminance level of the gap between the double flashes to a value at which the subject performed consistently at 80 to 85% correct responses. During these and the subsequent training sessions the payoff matrix was set at three cents for each correct response (hits and correct omissions) and minus three cents for each error (false alarms and misses). After each 100-trial run the experimenter gave the subject the results of that run, including d' and β, earnings for the run, and the various percentages of errors and correct responses. Computations of d' and β were derived from percentages of errors and correct responses from published tables [3,10]. Subjects could earn additional money for consistency of performance within a session. If the average d' and β computed over all individual runs in one session, except for the first run of the session, had standard deviations of less than 0.2, the subject could earn a bonus of 10% of his earnings on that session for each measure so determined. An additional 10% could be earned if the standard deviation of both measures for that session were below 0.1. Thus, the subject could earn up to 40% more each session by increasing consistency of performance within a session.

Receiver Operating Characteristic Determination

After the subject's performance had stabilized, data for construction of the ROC was collected by changing the payoff matrix. In addition to the equal bias matrix used during training, two other matrices were used, one favoring adoption of a strict criterion, the other of a lax criterion for maximum earnings. These matrices paid off hits and omissions at 5 cents and 1 cent respectively and penalized false alarms and misses at -1 cent and -5 cents respectively when adoption of a lax criterion was desired. A rotation of this matrix when a strict criterion was desired paid the subject maximally for correct omissions and penalized him heavily for false alarms. Data from five to fifteen runs (up to 1500 trials) were collected for each point on the ROC. Subjects received feedback about performance after each run during this phase. Subjects were given one 2-hr session with the equal bias matrix with no feedback prior to the first of the drug sessions.

Drug

Three subjects who were able to achieve d' standard deviations of 0.25 or less on the equal bias matrix during the training and ROC determination stages continued on to the drug phase of the experiment. They were tested individually. Subjects arrived at the laboratory after a 12-hr fast where EEG electrodes at O_Z and C_Z (International 10–20 System) referenced to right earlobe were attached. The EEG was amplified by Grass 7P511 amplifiers (response 3dB down at 0.1 Hz and 0.1 Khz) and the amplified signals were digitized by a set of multiplexed A/D converters controlled by a DEC PDP 11/40 computer and stored on magnetic disk for later analysis. After 15-min of light adaptation in the test room the subject received two pre-drug baseline runs. A physician then administered 0 mg (placebo), 5 mg or 10 mg of methadone orally, double-blind. The subject was tested at 10 min, 60 min, 90 min, 120 min, 180 min, 240 min, and at 2-hr intervals thereafter. Two 6-min runs separated by a 5-min rest constituted each drug day test period and the statistics computed from each of the runs were averaged to produce each data point. Although the total time to produce each data point was 17 min, times given in this report refer to the starting time of each pair of runs.

Subjects received no feedback about performance during the drug sessions except the total amount of earnings at the end of the day. All runs during drug sessions were with the

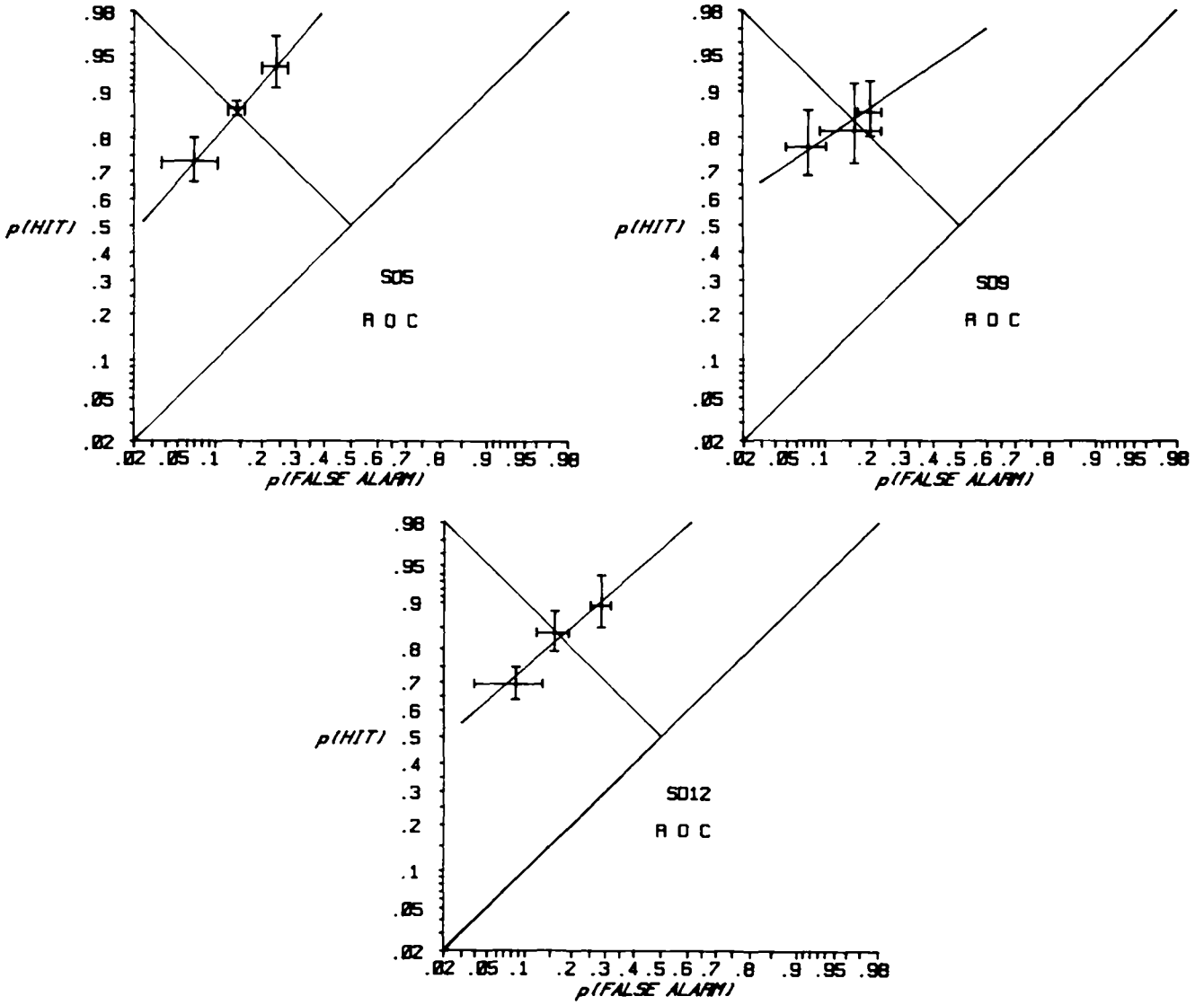

FIG. 1. Receiver Operating Characteristic for each subject generated under three conditions of payoff. A straight line fit of the three points which is parallel to the long diagonal indicates that the assumptions of underlying Gaussian distributions of equal variance are met.

equal bias payoff matrix. At least seven days separated each successive drug session.

RESULTS

Three subjects attained sufficient consistency of performance to advance to the drug phase. The ROC's of these three subjects are plotted as percentage of hits against percentage of false alarms for each of the three payoff conditions prior to drug testing. Figure 1 shows these functions plotted on normal-normal axes. The intersection of each of the crosses represents the average of the hit rate and false alarm rate computed over one or several sessions at any given payoff matrix. The vertical and horizontal extensions of the crosses indicate ± 1 standard deviation. The greater the distance of any point from the long diagonal (chance performance line), the better the performance on the task. The greater the distance of any point from the short diagonal (equal bias line), the more lax (above the line) or the more strict (below the line) the criterion.

Since these functions are plotted on normal probability distribution axes, the more nearly the three points on each plot are fitted by a straight line, the closer the signal space approximates a Gaussian distribution. Similarly, the closer the slope of the ROC function is to one (parallel to the chance performance line, the long diagonal), the more nearly correct is the assumption of equal variance for the signal plus the noise and the noise-alone distributions.

Figure 2 shows the response of one subject before and after taking 10 mg of methadone. Performance at various times relative to drug administration is indicated by the letters on the plot. Performance pre-drug, and out to 60 minutes post-drug, differs little from data collected to plot the ROC (see Fig. 1 for comparison). From 90 min to 180 min performance falls toward the chance performance line along

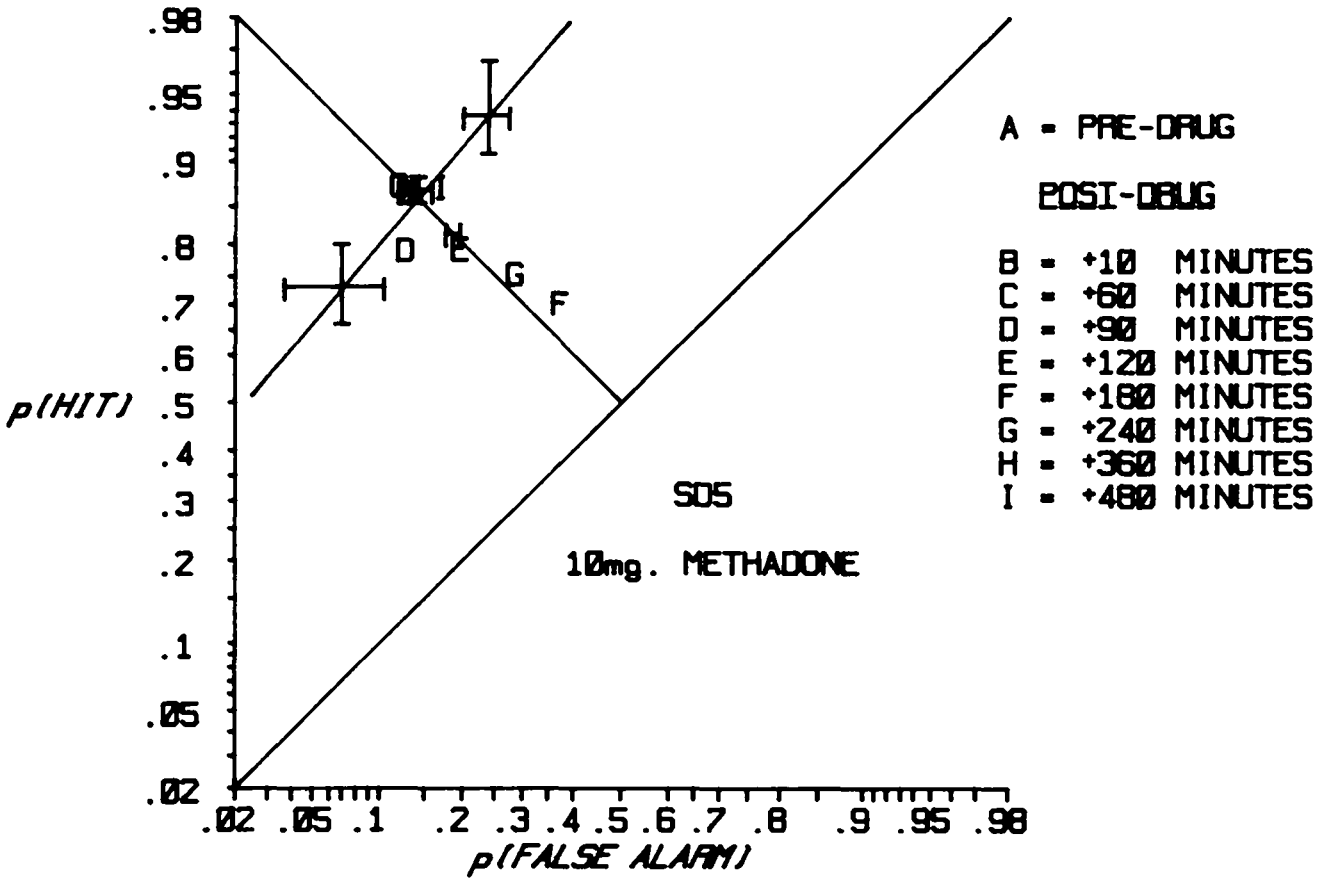

FIG. 2. Performance change after 10 mg oral methadone. Note that the change in performance is mostly along the short diagonal, indicating that methadone reduces visual sensitivity without substantially changing subject criterion.

the equal bias baseline. Recovery is virtually complete by 480 min.

Although a plot of performance after drug against the ROC of each subject gives a clear picture of how the drug affects both detection sensitivity and criterion, this method provides neither a good view of drug effect with time nor the dose-response relationship. Since the ROC's of each subject indicate a close approximation to the assumptions of normality of signal space and equal variance of the two distributions, the data can be plotted using the derived measures d' and β with little error.

Figure 3 shows changes in sensitivity and in criterion after various doses of methadone in the three subjects. While there are clear differences between subjects in the degree of drug effect, all subjects show an increasingly larger peak sensitivity deficit with increasing dose. Duration of action is longer with increasing dose. The period of drug effect on d' is coincidental with subjective feelings of drug action. The figures indicate little systematic change in bias with methadone.

Analysis of Evoked Potential Data

Averaged evoked potentials were computed from each lead to each stimulus-response combination. Computations of the variance of amplitude at each time point on the evoked potentials enabled the construction of confidence limits about each waveform which were used to determine at what time points two waveforms differed significantly from each other. In this report, we show waveforms collected when subjects responded correctly to the double flash stimulus.

Figure 4 exhibits averaged evoked potentials of the subjects. Predrug evoked potentials from the occipital lead are compared both with evoked potentials at peak behavioral effect and with evoked potentials recorded at the time when behavioral performance had returned to predrug levels. Level differences on the solid line below each pair of evoked potentials indicate where the 90% confidence intervals about both waveforms did not overlap.

The change in evoked potentials at peak behavioral effect is similar for all subjects. The significant differences as a result of drug at the vertex lead are nearly the same as those shown on the occipital lead. The differences can be noted as early as 100 msec after the onset of the first bright flash. A second period of evoked potential alteration with drug occurs within 200 msec of the occurrence of the second flash.

Although overall behavioral performance was lower at time of peak drug effect than predrug, the evoked potentials shown in Fig. 4 were collected only when the subject correctly identified the gap stimulus. Since behavior (correctly pressing the button) was the same in the two periods

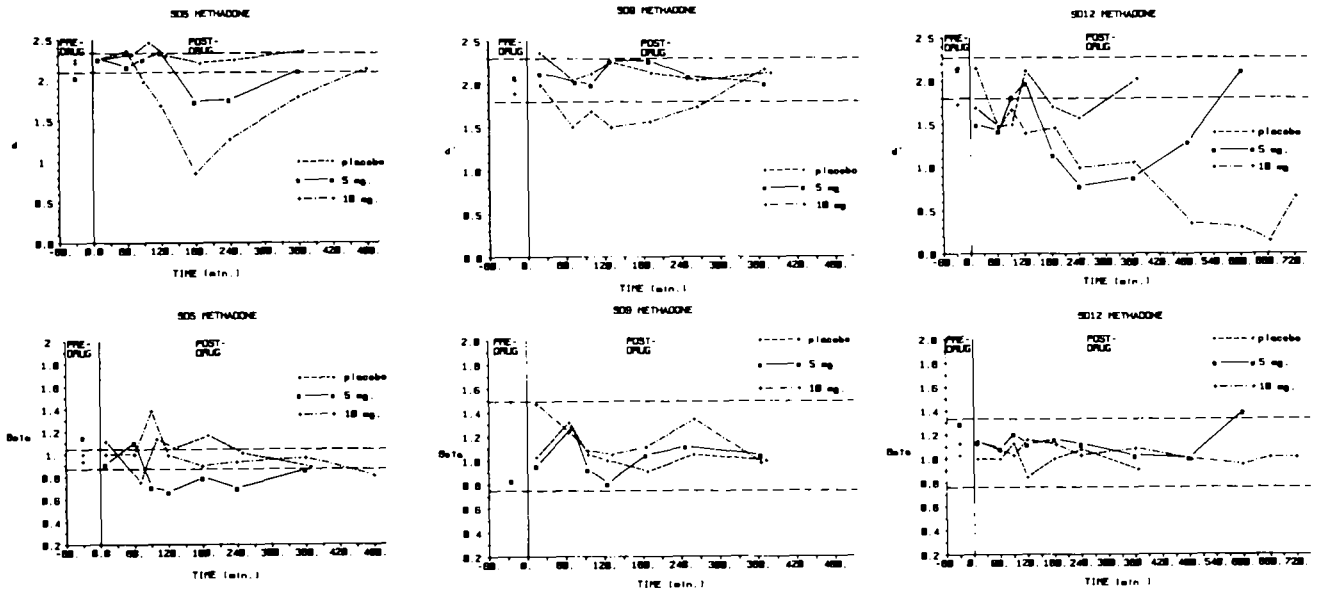

FIG. 3. Derived statistics d' (sensitivity) and β (bias) plotted as a function of time after each dose of methadone. The parallel, dashed horizontal lines indicate ± 1 standard deviation about the mean value of each statistic computed from the data with the equal bias payoff matrix on the ROC determination sessions. Note the change in time scale for subject SD12.

for the evoked potential data here, and since the average latency to motor response was over 700 msec from the onset of the initial flash, the significant differences between evoked potentials collected pre- and postdrug may be attributed to a drug effect on a sensory system.

DISCUSSION

The individual differences in both the magnitude and duration of the depression in detection performance are reminiscent of the large subject-to-subject variability in response to opioids in general. Subject differences in reactivity to opioids are both quantitative and qualitative [6]. Thus different subjects need different doses for the same degree of analgesia and some subjects may experience euphoria, whereas others may experience dysphoria. It should also be noted that fixed doses of drug were used in this study, although the body weight of our subjects ranged from 65–90 kg. Our protocol limited us to a maximum of 10 mg per subject. The data presented here are not claimed to represent typical dose-response curves of humans to methadone, but only to demonstrate that methadone can specifically depress visual function.

Despite the individual differences in response to drug, the depression of visual sensitivity after methadone was striking. The Theory of Signal Detectability design points specifically to a drug effect on a sensory process, rather than on the subject's ability to evaluate the information reaching him. Changes in pupil size are not responsible for the depression in double flash detection performance. Significant changes in the evoked potential at peak drug effect indicate that a response to the drug is evident at visual cortical areas. An entry point for methadone, or for methadone-induced electrical or neurochemical effect on the visual system, may lie somewhere between the pupil and the visual cortex.

Several areas of the brain which are known to subserve visual function are also known to bind opiates. In the monkey brain, little opiate binding was found in the occipital cortical areas, while heavier concentrations were found in the lateral thalamus and superior colliculus [13]. Similarly, in the rat brain, there is evidence of binding in the superior colliculus and ventral (but not dorsal) nucleus of the lateral geniculate, the nucleus of the optic tract in pretectum as well as all three nuclei and fibers of the accessory optic tract [1,2].

Opioids may affect visual function through action on more distant cells which in turn contact and possible modulate cells in the visual system. Interesting in this respect are the effects of opiates on release and turnover of neurotransmitters. Release and turnover rates of dopamine in the CNS are increased by opiates [4,18], although the mechanism for this increase is still in dispute. While dopaminergic neurons are not widespread in the visual system, significant concentrations of them are known to be present in the retina of a wide variety of mammalian and non-mammalian species [5,9,17]. Most dopaminergic cells in the retina are found in the inner nuclear layer where they appear to be similar to the neighboring amacrine cells, comprising up to 10% of the total number of such cells. The release of dopamine in the retina to light stimulation and its likely role there as an inhibitory neurotransmitter has been demonstrated [11,12]. If opiates induce increased turnover of dopamine in the retina, as they do in other parts of the CNS, and the increased turnover of dopamine has postsynaptic consequences, then an opiate effect on dopamine neurons in the retina becomes a likely candidate for explaining the depression of visual performance and scalp-recorded light evoked potentials reported above.

Opioids may exert their effects on dopamine metabolism through the association of opiate receptors with dopaminergic neurons. Binding sites for Leu-enkaphalin, an opioid peptide, in close association with dopaminergic neurons in

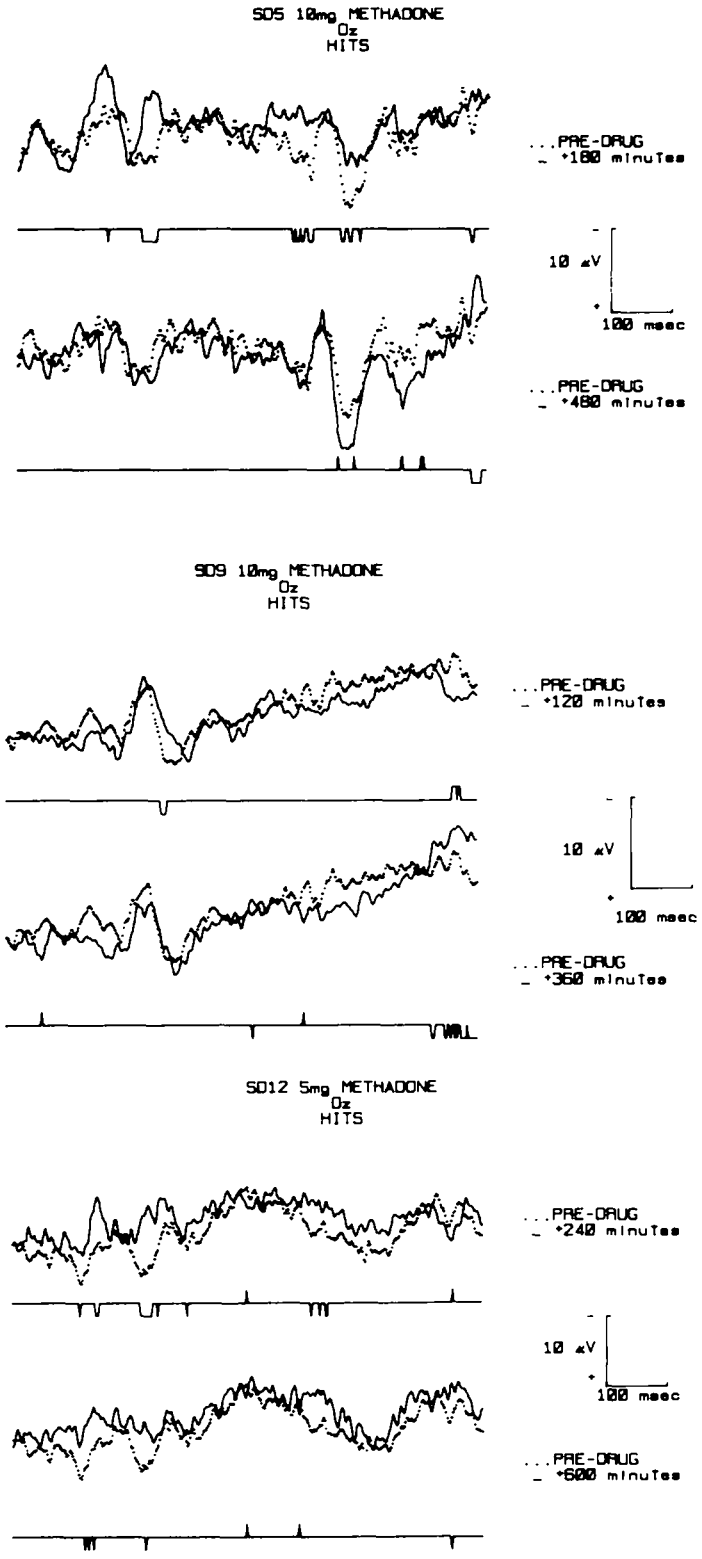

FIG. 4. Averaged evoked potentials recorded from monopolar midline occipital (O_z) leads to double flash stimuli to which the subjects correctly responded. The solid, three level horizontal line directly below each pair of waveforms indicates the time points at which the two waveforms are significantly different. Data was digitized at 2 msec intervals starting 10 msec before stimulus onset.

striatum have been shown [19]. Opiate binding sites have been identified in homogenized retina [16]. Should opioids be shown to alter dopamine turnover in the retina, a search for locations of opioid binding sites in the retina might prove fruitful.

Regardless of the source of opioid activity in the visual system, it is clear that opioids can affect visual function. Investigators studying opioid effects of more complex CNS function and on behavioral mechanisms such as arousal, activation and attention often use visual stimuli to gain access to their subjects. The contribution of drug-induced alteration in sensory function must be accounted for in any such demonstration.

ACKNOWLEDGEMENTS

We wish to acknowledge the technical assistance of Dr. J. Albeck, Dr. John Kuehnle, Dr. Roger Meyer, and the nursing staffs of Bowditch II and Oaks II, McLean Hospital.

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