sponds to the higher cut-off frequency at any flicker amplitude. But in the actual measurements, it is only because the slower process is psychophysically more sensitive than the faster one that both can be detected by appropriate manipulations. Thus, at a fixed amplitude in Fig. 2 (for example, 1000 trolands), the cut-off frequency for the adapted condition is much lower than in the fully modulated condition.

However, the slower, unadapted process that governs all the classical flicker thresholds (*6*) never appears in the LRP or electrical-phosphene data. Our results support the explanation that this psychophysical flicker envelope represents a further stage of temporal filtering proximal to the photoreceptors. Both of these stages seem to be controlled by some type of distributed filter mechanism.

D. H. KELLY
Stanford Research Institute, Menlo Park, California 94025
R. M. BOYNTON
Department of Psychology, University of California at San Diego, La Jolla 92037
W. S. BARON
Stanford Research Institute, Menlo Park

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20. Linearity requires the amplitude response (ΔB) to be independent of the background (B). Therefore, Weber's law ($\Delta B \sim B$) is a form of nonlinearity.
21. Part of this loss of sensitivity can be attributed to the bleaching of cone pigments. W. A. H. Rushton and G. H. Henry [*Vision Res.* **8**, 617 (1968)] found a half-bleach constant of 20,000 trolands, which would displace the 48-hertz point below the upper solid line in Fig. 2 by a factor of about 2.2. The remainder of the loss must involve other adaptive effects that also obey Weber's law (*17*).
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Time-Dependent Disruption of Morphine Tolerance by Electroconvulsive Shock and Frontal Cortical Stimulation

Abstract. *Electroconvulsive shock or frontal cortex stimulation administered to rats at 5 but not at 180 minutes after an initial administration of morphine sulfate disrupted the development of one-trial tolerance to the analgesic effects of morphine sulfate. It is suggested that development of tolerance may be mediated by cellular mechanisms and memory processes similar to those thought to underlie conventional learning.*

A number of investigators (*1*) have suggested that tolerance to morphine may represent a form of learning which may be mediated by memory processes and cellular mechanisms similar to those underlying conventional learning. Support for this position comes from a series of studies showing that protein synthesis inhibitors attenuate or abolish not only retention of a number of learning experiences, but also tolerance to morphine as revealed in tests for analgesia (*2*).

One presumed characteristic of memory is that a consolidation process is required for efficient storage of newly acquired experiences. This consolidation process is inferred from studies demonstrating that specific treatments such as electroconvulsive shock (ECS) or discrete brain stimulation are capable of producing a time-dependent disruption in long-term retention of recent experiences (*3*). In other words, an ECS treatment is capable of disrupting long-term retention when applied immediately after a learning experience, but becomes increasingly ineffective when delayed a few minutes or a few hours. Thus, the present study examined the possibility that the development of tolerance to analgesic effects of morphine is also mediated by time-dependent processes (perhaps similar to consolidation), by administering ECS immediately, or after various delays, subsequent to an initial morphine experience. We found that ECS or frontal cortex stimulation treatments can, on a time-dependent basis, disrupt the development of morphine tolerance.

Since previous research (*4*) has demonstrated that morphine tolerance can develop following a single dose (one-trial), it was possible in the present study to examine the effects of ECS on the temporal course of tolerance development. Fifty-eight male Long-Evans rats were divided into seven groups. All experimental groups received initial injections of saline or morphine sulfate (30 mg/kg, intraperitoneally). The initial dose of 30 mg/kg was selected because in our laboratory it represented the threshold dose above which there was a high incidence of mortality. Forty-eight hours later animals received injections of saline or morphine sulfate (15 mg/kg, intraperitoneally), followed 30 minutes later by a standard test of analgesia (*5*). The morphine test dose of 15 mg/kg was selected because at that level the greatest difference in responsiveness to shock (analgesic test) was found between saline- and morphine-injected animals. This difference was not as pronounced at other morphine dose levels.

The first group (N = 8, M-M) received the initial morphine (30 mg/kg) injections followed 48 hours later by the second morphine injection (15 mg/kg). The second group (N = 8, S-M) was injected with saline followed 48 hours later by morphine. The third (N = 8), fourth (N = 8), and fifth (N = 8) groups (M-ECS-M) received initially morphine followed either 5, 60, or 180 minutes later by an ECS (35 ma, 0.5 second duration) treatment administered through earclips attached to the pinnae. The sixth group (N = 10, ECS-M-M) received an ECS treatment 5 minutes prior to the initial morphine injection. Forty-eight hours later, the third, fourth, fifth and sixth groups of animals received the second injection of morphine (15 mg/kg). The last group (N = 8, S-S) received two injections of saline spaced 48 hours apart.

Thirty minutes after the second injection all animals were given a shock threshold test to determine their sensitivity to pain. Each animal was introduced and adapted for 1 minute to a small box with a grid floor. After the adaptation period, foot shocks (starting with 0.1 ma intensity) were delivered in ascending order of shock intensity until jump and squeal responses were observed for three consecutive foot shocks or until a 10 ma intensity was reached. Shocks were delivered via a constant current scrambler for 0.5 second; pulse repetition rate was 200 hertz and 4 msec pulse duration. From 0.1 to 1.0 ma successive test shocks were increased by 0.1 ma, and from 1.0 to 10 ma by 0.2 ma. The intershock interval was approximately 6 seconds, but shocks were delivered only when the animal was making contact with the grid floor with all four paws. The behavioral responses to each shock

were observed and recorded by an experimenter who was blind to prior treatment conditions. The shock intensities required to initiate "flinch," "jump," or "jump and squeal" responses and reach the criterion of three consecutive jump and squeal responses were used as dependent measures. A "flinch" was defined as a response to shock characterized by crouching or a rapid change in posture without any concomitant movement of the paws. A "jump" was characterized by rapid raising of one or more paws often followed by rapid running. A "jump and squeal" was characterized by the combination of jumping and two or more detectable vocalizations.

The mean shock intensities for the flinch, jump, and jump and squeal thresholds and criterion for all the groups are shown in Table 1.

The data were analyzed with a one-way analysis of variance which indicated that for the flinch threshold measure there were no significant differences among the groups, but for the jump threshold ($F = 2.8$, d.f. = 6/51, $P < .05$), jump and squeal threshold ($F = 6.8$, d.f. = 6/51, $P < .01$), and criterion measure ($F = 4.9$, d.f. = 6/51, $P < .01$), there were significant differences among the groups.

Since the pattern of results for jump threshold, jump and squeal threshold, and criterion measures were similar (see Table 1), a more detailed analysis with a Duncan Multiple Range Test is presented only for the jump and squeal threshold data. These tests revealed that (i) morphine at 15 mg/kg indeed produces an analgesic effect, as indicated by a higher mean jump and squeal threshold for the S-M group compared to the S-S group ($P < .01$); (ii) tolerance to morphine analgesia can be acquired in one trial as indicated by the significant reduction in mean jump and squeal threshold of the M-M group relative to the S-M group ($P < .01$) and no reliable difference compared to the S-S group; (iii) ECS administered 5 minutes after the first morphine injection disrupted the development of tolerance, as indicated by both a significant increase in mean jump and squeal threshold relative to the M-M group ($P < .01$) and by maintenance of a similar threshold level in comparison with the S-M group; (iv) ECS administered prior to a morphine injection fails to disrupt the development of tolerance, as indicated by a mean jump and squeal threshold similar to that of the M-M group and a significantly lower threshold compared with the 5 minutes M-ECS-M group ($P < .05$) and the S-M group ($P < .01$). This latter observation suggests that ECS has specific effects upon biochemical events following a morphine injection, which by some mechanism must be related to development of tolerance; and (v) ECS administered 180 minutes after the first morphine injection fails to disrupt development of tolerance, as indicated by a mean jump and squeal threshold similar to that of the M-M group and a significantly lower threshold compared to the S-M group ($P < .01$) and the group that received ECS 5 minutes after the morphine injection ($P < .01$). This latter finding suggests that the disruptive effects of ECS are time-dependent and eliminates possible proactive effects of ECS as the determiner for producing a disruption of morphine tolerance.

Thus, tolerance to the analgesic effects of morphine is susceptible to ECS interference on a time-dependent basis in a way at least superficially similar to more conventional learning situations, suggesting the possibility that a process similar to consolidation may be associated with the development of morphine tolerance.

In recent years, many investigators have demonstrated that direct, low-intensity, subseizure levels of electrical stimulation of specific brain regions is sufficient to produce a time-dependent retrograde amnesia for a variety of learning experiences (*3*). It was, thus, of interest to stimulate specific neural regions that may be directly or indirectly related to development of morphine tolerance. The frontal cortical region and caudate nucleus were selected because they contain a reasonable (although not the largest) amount of opiate receptor (*6*) and because post-trial electrical stimulation of caudate or frontal cortex can produce disruption of long-term retention (*7*).

Table 1. Mean shock intensities for "flinch," "jump," and "jump and squeal" thresholds and criterion as a function of ECS treatment in rats.

Groups				*N*	Mean flinch threshold (ma)	Mean jump threshold (ma)	Mean jump and squeal threshold (ma)	Mean criterion (ma)
Treatment	First injection	Treatment	Second injection					
	Morphine		Morphine	8	0.5	1.4	2.1	3.3
	Saline		Morphine	8	1.1	3.6	6.6	7.0
	Morphine	ECS*	Morphine	8	0.5	2.7	5.8	6.6
	Morphine	ECS†	Morphine	8	.7	2.5	4.1	5.7
	Morphine	ECS‡	Morphine	8	.5	1.4	2.4	3.1
ECS§	Morphine		Morphine	10	.5	1.6	3.3	4.2
	Saline		Saline	8	.4	1.1	1.2	1.7

*Given 5 minutes after the first injection. †Given 60 minutes after the first injection. ‡Given 180 minutes after the first injection. §Given 5 minutes prior to the first injection.

Table 2. Mean shock intensities for "flinch," "jump," and "jump and squeal" thresholds and criterion as a function of localized brain stimulation in rats.

Groups			*N*	Mean flinch threshold (ma)	Mean jump threshold (ma)	Mean jump and squeal threshold (ma)	Mean criterion (ma)
First injection	Treatment	Second injection					
Morphine	None	Morphine	11	0.7	2.0	3.3	4.1
Morphine	Stimulation of frontal cortex*	Morphine	7	.5	1.8	7.4	8.3
Morphine	Stimulation of frontal cortex†	Morphine	8	.5	1.7	5.2	6.5
Morphine	No stimulation; frontal cortex implanted	Morphine	10	.5	1.5	4.3	5.9
Morphine	Stimulation of caudate nucleus*	Morphine	5	.7	1.7	3.8	5.6

*Given 5 minutes after the first injection. †Given 180 minutes after the first injection.

Under Nembutal anesthesia 30 Long-Evans male rats had bilateral implants of bipolar plastic products (No. MS-303, 0.025 cm in diameter) cranial plugs placed into the frontal cortical region ($N = 25$) (coordinates 2.0 mm anterior to Bregma, 2.5 mm lateral, and at the surface of the brain) and into the caudate nucleus ($N = 5$) (coordinates 0.5 mm anterior to Bregma, 2.5 mm lateral, and 5 mm vertical); measurements were taken from a level skull. The electrode assembly was fixed to the skull with acrylic cement. Another eleven rats did not undergo any surgery. At least 2 weeks after recovery from surgery, all animals received the initial injection of morphine (30 mg/kg) followed either 5 minutes later ($N = 7$) or 180 minutes later ($N = 8$) by bilateral frontal area stimulation (eight 5-second trains of biphasic pulses with 10 seconds between trains at an intensity of 1.5 ma, 100 hertz, 1 msec duration), or, 5 minutes later, by bilateral caudate stimulation ($N = 5$) (eight 5-second trains of biphasic pulses with 10 seconds between trains at an intensity of 500 μa, 30 hertz, 1 msec duration), or no stimulation for the frontal implanted ($N = 10$) and the nonoperated ($N = 11$) groups. Electrical stimulation was delivered via two Nuclear-Chicago constant-current stimulators. Electrographic activity was recorded from the frontal cortical region or caudate electrodes immediately after stimulation offset. At the stimulation levels employed, no seizure afterdischarges or other electroencephalographic abnormalities were recorded. Forty-eight hours later all rats received an injection of morphine (15 mg/kg) followed 30 minutes later by the test for analgesia (*8*). The mean shock intensities for the flinch, jump, and jump and squeal thresholds, and criterion for all the groups are shown in Table 2.

The data were analyzed with a one-way analysis of variance which indicated that there were significant differences among the groups only for the jump and squeal measure ($F = 3.1$, d.f. = 4/36, $P < .05$). A Duncan Multiple Range Test revealed that frontal cortical region stimulation applied 5 minutes but not 3 hours after the first morphine injection disrupted the development of tolerance as indicated by a significant increase in mean jump and squeal threshold relative to unoperated and operated controls ($P < .01$ and $P < .05$ respectively). The results of frontal cortical stimulation therefore suggest that the frontal cortical region and interconnected neuronal systems may play a role in the development of morphine tolerance. Caudate nucleus stimulation did not disrupt morphine tolerance. However, the failure of caudate nucleus stimulation to disrupt morphine tolerance could have been due to inappropriate selection of frequency or intensity parameters, or both, or due to the strong possibility that different neuronal regions mediate different kinds of learning experiences (*3*).

In conclusion, the data from both the ECS and discrete brain stimulation experiments provide additional support for a possible parallel between conventional learning and tolerance to drugs.

RAYMOND P. KESNER
D. J. PRIANO
J. R. DEWITT
Department of Psychology,
University of Utah,
Salt Lake City 84112

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8. At the termination of the experiments all rats were anesthetized with Nembutal and perfused pericardially with saline and formal-saline. The brains were cut at 50-μ sections through the electrode tracks and were stained with cresylviolet. Results are presented only for histologically verified placements in frontal cortex and caudate nucleus.
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Perceptual Analysis of Moving Patterns

Abstract. *Configurations of moving points are often perceptually analyzed into relative and common vectors that are different from the actual motions. If a movement configuration is abruptly replaced by a test point whose objective velocity continues the apparent (but illusory) course of one of the original points, observers perceive that course as uninterrupted and colinear. This finding provides a quantitative measure of the vector extraction phenomenon and was used to show that neither of the two current models adequately fits that phenomenon.*

Johansson and his colleagues (*1, 2*) have shown that, in configurations of moving elements that share common motion components, one *common* vector becomes the frame of reference for residual component motions (Fig. 1). The rows of spots labeled A and C move from left to right, while B moves between them along a diagonal path. If the horizontal component of B's motion equals that of A and C, and if this configuration is viewed against a homogeneous black background, the diagonal motion of B becomes almost impossible to discern (*1*). Instead, B appears to move vertically between A and C, while the whole system of spots, ABC, may also be perceived as moving to the right.

The phenomenon of perceptual vector extraction is not merely a laboratory curiosity. It has been taken as an example of the visual system's sensitivity to higher-order variables of stimulation (*3*), as the basis for much of the observer's information about his movements in his environment (*2*), and as an important component of tridimensional space perception (*2, 3*). To Johansson, the process is a direct vector analysis, performed automatically by the perceptual system on the entire visual field. Stoper (*4*) has suggested, however, that the phenomenon has a peripheral explanation, that it occurs because the eye pursues the common vector, and that what we perceive is simply the residual movement that the pursued stimulus then projects to the retina of the eye.

We now describe a quantitative measure of the phenomenon of vector extraction that calls into question the adequacy of both earlier explanations. In Fig. 2, the pattern of moving elements is the same as that in Fig. 1, until some time t_1. At that time, rows A and C are deleted and, simultaneously, element B changes its path to the vertical ($\theta = 90°$). If B's motion, before t_1, is really perceived as vertical (and if the effect of the moving framework ceases when A and C are deleted), then B's motion should appear to be continuous and colinear between movements *ii* and *iii*, even though that is not the physical situation.