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Ethanol's Effects on Tremor and Positioning in Squirrel Monkeys*

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ABSTRACT. Ethanol ingestion markedly reduces tremor in patients with essential tremor. This clinical observation prompted the present experiments, which were designed to investigate ethanol's reduction of tremor in squirrel monkeys trained to execute a bar-holding task. A lever was attached to the hub of a rotary variable differential transformer (RVDT) and three squirrel monkeys were trained to position this lever within a 4.5 cm band for 8 seconds for a fruit juice reward. Behavior was maintained by a random ratio 2 schedule of reinforcement. Angular position of the lever was sampled for 5.12 seconds while the monkey held the bar, differentiated twice and analyzed to obtain a spectral description of tremor in units of acceleration^2/Hz. During control and vehicle sessions a spectral peak appeared at about 6-8 Hz and the magnitude of this peak varied from 25 to 150 milli-g^2/Hz (where g is the acceleration due to gravity). A second peak appeared in two animals at greater than 15 Hz. For one animal this high-frequency peak was dominant during control sessions but the 6-8 Hz peak was dominant after intubation with water or ethanol. Ethanol produced consistent and dose-related decreases in the amplitude of the spectrum describing tremor but the location of the spectral peaks did not differ from vehicle sessions. The doses that altered tremor also produced an increase in the number of short-duration holds as well as other, less consistent, alterations in the form of the response. These data confirm and quantify ethanol's potency as a tremorolytic agent. (*J. Stud. Alcohol* **52:** 492-499, 1991)

WHEN AN OUTSTRETCHED HUMAN HAND is carefully observed, normal tremor appears as small oscillations in position. An accelerometer attached to this limb measures these oscillations as the second derivative of position, or acceleration (Newland, 1988). Spectral analytic techniques reveal that these oscillations occur over a wide band of frequencies but, in most normal humans, there is a peak in the power spectrum in the range of 6-8 Hz. A second mode is often seen between 15 to 25 Hz, and spectra with even more peaks have been reported (Elble et al., 1987; Marsden et al., 1969; Wood et al., 1973; Wyatt, 1968). The multiple modes could reflect contributions from different sources. The arm, hand and finger might be expected to oscillate at different rates because of their different masses (Randall and Stiles, 1964; Stiles and Randall, 1967), and broad-band, high-frequency deviations could reflect the firing of motoneurons (Freund, 1983; Freund et al., 1984a,b) or specific pharmacological intervention (Fowler et al., 1990).

The frequency of the dominant acceleration varies over a narrow range when compared across healthy individuals and is quite stable when measured at successive times within the same individual (Marsden et al., 1969). The location of the dominant frequency, or the absence of movement within a band of frequencies, can be diagnostic of certain nervous system disorders, or may reflect pharmacological manipulations. For example, high-amplitude tremor at frequencies less than 6 Hz reflects disorders such as Parkinson's disease or peripheral neuropathies (Marsden, 1984), while the absence of power in the 6 to 8 Hz band has been associated with muscular dystrophy (Freund et al., 1984a,b).

Clinical experience has revealed that a small amount of ethanol provides substantial relief from essential tremor. As little as a single glass of wine may moderate or even eliminate essential tremor (Fahn, 1984; Marsden, 1984; Young and Shahani, 1979). Within 15 minutes of ingesting only 15 to 25 g of ethanol (about 0.2 to 0.35 gram/kg), patients with essential tremor experience relief for up to several hours (Growdon et al., 1975; Rajput et al., 1975). Often, however, these patients also report a transient increase in tremor after ethanol's tremorolytic action has passed. Ethanol's action seems to be limited to essential tremor; it is much less effective, or completely ineffective, in patients with action tremor, Parkinsonian tremor or other tremors resulting from specific lesions (Rajput et al., 1975; Koller and Biary, 1984).

Ethanol's powerful influence on essential tremor suggests that an understanding of these effects might provide clues to the sources of ethanol's other, more widely

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known, effects on motor function. This suggestion is further supported by studies that suggest that tremor reflects several distinct features of motor function, including the integrity of the neuromuscular junction (Freund et al., 1984a), the speed with which a limb can move (Freund, 1983; Freund et al., 1984b) or initiate movement (Goodman and Kelso, 1983), and the presence of nervous system disorders (Marsden, 1984).

The use of tremor as an index of motor function carries many advantages (Newland, 1988). Tremor is a replicable and quantifiable phenomenon. Spectral analytic descriptions of tremor quantify it by breaking movement down into different component frequency bands of different magnitudes. This analytic technique permits one to associate specific alterations in tremor with pathological states, pharmacological intervention or exposure to toxic substances (Freund et al., 1984a,b; Gerhart et al., 1982; Gothoni, 1985a,b; Herr et al., 1985; Newland, 1988; Young and Shahani, 1979).

Considering both the advantages of quantifying tremor and the sensitivity and specificity of this endpoint to ethanol, it is surprising that there are so few studies of ethanol's effect on tremor. The human studies cited above demonstrate the potency of ethanol in reducing the amplitude of essential tremor, but few studies have quantified this endpoint with appropriate measures such as spectral analysis, or attempted to relate ethanol's acute effects on tremor to other aspects of motor function. Tremor's sensitivity to ethanol in humans suggests that it might be possible to detect changes in tremor at doses below those which produce gross incoordination, ataxia or sedation.

The present study was undertaken to investigate ethanol's reduction of tremor in healthy squirrel monkeys trained to execute a bar-holding task. This task was designed to enable the simultaneous characterization of tremor and other aspects of behavior and motor function. The technique of assessing tremor with a bar-holding task was validated by examining drug-induced increases and decreases in tremor, by comparing the shape and magnitude of the spectra describing tremor with the extant literature and by comparing tremor taken from a human pressing a load cell with tremor taken from the same human executing the bar-holding task (Newland, 1988).

Method

Subjects

Three female squirrel monkeys (*Saimiri sciureus*) at least 9 years old and weighing 0.5 to 0.6 kg were used. The animals were maintained in the University of Rochester vivarium, a facility approved by the American Association for Accreditation of Laboratory Animal Care, and in an earlier study (Newland and Weiss, 1986) had been administered oxotremorine in acute doses up to 1 mg/kg. The monkeys were allowed access to water for 1 hour in the late afternoon, which, combined with the juice earned during experimental sessions, provided sufficient fluids to maintain their body weight.

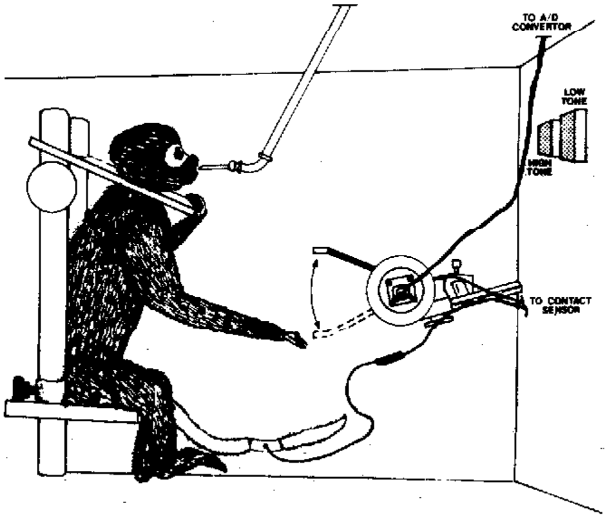

FIGURE 1. An illustration of a squirrel monkey and the response bar. The bar is insulated everywhere except the handle to restrict the response topography. A contact sensor attached to the monkey's tail and the bar registers when the bar is gripped. Bar position is digitally converted and stored for later analysis. When the bar is held in range, a low-frequency tone sounds. Every completed response results in a high-frequency tone burst and, on a random-ratio 2 schedule of reinforcement, a squirt of juice.

Apparatus

During the experimental session, the monkey sat in a small primate chair situated about an arm's length from a lever that was positioned in front of a stimulus panel containing lights and speakers (Figure 1). These components were housed in a sound-deadened chamber. White noise was provided throughout the session to mask extraneous sound. The response device was a counterbalanced hollow aluminum rod weighing about 1.3 grams and attached to the hub of a rotary variable differential transformer (RVDT) that provided an analog voltage proportional to angular displacement. (Note: The conventional abbreviations for grams and for acceleration due to gravity are the same. To avoid confusion, "grams" will be spelled out and an italic *g* will be used for acceleration due to gravity.) Manufacturer's specifications list the maximum drag on angular movement as less than 1 gram-cm and the moment of inertia as 0.615 mg-cm/sec^2. The rod was counterbalanced so that when released it returned approximately to a horizontal position. The rod was electrically insulated everywhere except the handle. A contact sensor attached to the monkey's tail and the response bar was used to detect when the monkey gripped the bar. The gain of the contact sensor was adjusted empirically to ensure that the monkey gripped the bar firmly by wrapping its fingers around it; light touches were inadequate to activate the sensor.

On-line control and measurement of all events and of the onset and offset of analog-to-digital (A/D) sampling was accomplished with 0.01 second resolution by a SKED-11 system (Snapper et al., 1982) manufactured by State Systems, Inc. (Kalamazoo, Mich.), operating on a PDP 11/73 computer (Digital Equipment Corp., Maynard, Mass.).

Procedure

The subjects were trained to grip a bar and hold it within 15° of horizontal (30° band, 4.5 cm arc length) for 8 seconds to obtain a fruit juice reward. When the bar was gripped sufficiently firmly and held in range, a low-frequency (nominally 500 Hz) tone sounded. The tone turned off if the bar moved out of range or the monkey released it. Juice was delivered according to a random ratio 2 schedule of reinforcement; half of the completed responses resulted in the reinforcement cycle, consisting of a 1-second high-frequency (nominally 1,000 Hz) tone burst, followed by a 0.6 ml squirt of fruit juice. The other completed responses resulted in the high-frequency tone burst alone. Sessions were 30 minutes in length.

A/D sampling of angular position commenced 2 seconds after the monkey placed the bar in range and continued for 5.12 seconds provided the bar was held in range for that period. The 2-second delay was imposed to eliminate false starts and the initial movements associated with positioning the bar. Sampling ended 0.88 seconds before the onset of the reinforcement cycle and 1.88 seconds before the delivery of juice. This delay excluded physical movements associated with receiving the juice.

Drugs

Doses of 0, 0.125, 0.25, 0.5, 1.0 and 1.5 grams/kg of ethanol were diluted in tap water to a volume of 12 ml and administered by gastric intubation 15 minutes before the experimental session. At least two sessions at each dose were conducted. Doses of 0.5 grams/kg or greater were administered once weekly, on Wednesday or Thursday. Lower doses were administered twice weekly on Tuesday and Friday. These doses were administered first in a single ascending series and then in an irregular order. To acclimate the subjects to ethanol and to the intubation procedure, sessions following intubation of water and 0.5 and 1.0 grams/kg of ethanol were conducted before the data reported here were collected. Data from these familiarization sessions were discarded.

Behavioral measures

Two sets of distributions describing the pattern of responding were formed from interevent times. The "hold-time" distribution describes the time spent gripping the bar sufficiently firmly to activate the contact sensor. This measure corresponds to the "time-on-task" measure as defined by Fowler et al. (1984) and Fowler (1987). A single hold-time was simply the time between gripping the bar and releasing it, regardless of whether the bar was in the target range. The second distribution describing the response pattern was the time-on-target (TOT) distribution. This was the duration of time that elapsed between entering the target range while holding the bar and either releasing the bar or leaving the target range.

Signal processing

Bar position was sampled for 5.12 seconds beginning 2 seconds after contact. These data were used for spectral analysis. Releasing the bar or moving it out of range resulted in the termination of sampling. Thus, sampling of bar position occurred during a stable portion of the response.

Tremor was assessed using spectral analytic techniques described in Newland (1988) and described briefly here. Smoothed, tapered acceleration signals from criterion (8 seconds) holds and containing only frequencies below 25 Hz were used for tremor analysis. These signals were generated as follows. Angular position of the bar was filtered using an analog Butterworth filter that provided 24 db/octave suppression beginning at 50 Hz. This operation prevented aliasing, the artifactual appearance of unwanted, high-frequency signals in the band of investigation. The filtered signal was then digitally sampled at 100 Hz for 5.12 seconds. These sampling parameters provide a maximal bandwidth of 50 Hz and a spectral resolution of 0.195 Hz. The filtered digitized position signal was stored on a computer disk, and digitally differentiated twice to produce a signal proportional to acceleration. The onset and offset of sampling was tapered with a Hamming window to prevent high-frequency artifact (Otnes and Enochson, 1972) and the result was multiplied by 1.85 to account for the window's gain of 0.54 (Harris, 1978). The data were then low-pass filtered at 25 Hz (8th-order lowpass digital Butterworth filter) and down-sampled to a 50 Hz sampling rate. Filtering and down-sampling ensured that only frequencies up to 25 Hz were included in the analysis. Differentiating the signal emphasized frequencies relevant to an analysis of tremor while de-emphasizing slow drifts in position. Digital signal analysis was accomplished using ILS software from Signal Technology, Inc. (Goleta, Calif.).

The data that resulted from the above operation were converted to a power spectrum, which decomposes the variance (or power) in a time series of data into a set of discrete frequency components corresponding to different rates, or frequencies, of movement. A 64-point power spectrum was computed from the time series for each completed response. The log of the spectra from all control sessions (those preceding a drug session) was smoothed by the formula:

TABLE 1. Number of spectra in the mean spectrum for each condition

		SUBJECT	
Condition	SM831	SM832	SM834
Control	819	1,108	417
Vehicle	383	225	89
0.125 gram/kg	127	39	52
0.25	203	102	80
0.5	234	55	61
1.0	85	43	17
1.5[a]	49	3	1

[a] Spectral analyses were not conducted at this dose because of the limited number of spectra available from SM832 and SM834.

$$P(i) = 0.25*P(i - 1) + 0.5*P(i) + 0.25*P(i + 1)$$

where $P(i)$ is the power in the i'th frequency bin. This was reduced to a 32-point spectrum by using every other frequency estimate. Thus, the estimate at each frequency represents an average over a band that is 0.74 Hz wide and centered on that frequency. The ensemble average of the log of the smoothed spectra from all control sessions (those preceding a drug session) was produced by calculating the mean ± two standard errors of the mean (SEM) for each frequency bin across the transformed spectra. Spectra from the different dosing conditions were treated similarly: ensemble averages of the log spectra and two SEMs were computed for each dosing condition. The number of spectra that entered each ensemble average is listed in Table 1.

Statistics

Spectra after ethanol were compared with control conditions using techniques described by Bendat and Piersol (1971). The difference between two log-transformed spectra, divided by their standard error, is a chi-square variable with degrees of freedom equal to the number of frequencies entering the estimate. The p values reported are for individual comparisons of the average spectrum taken from an exposure condition with the average spectrum taken from control sessions, unless stated differently. The highest p value associated with spectra reported as "different" was .003 and typical values were much lower. The low p values and the consistency of the effects make it very unlikely that the effects reported are statistical artifacts resulting from multiple comparisons. "Hangover" tremor was investigated 24 hours after ethanol administration and compared with the same control session using the same techniques.

The hold-time and TOT distributions are presented as cumulative distribution functions in which the functions for all control sessions were combined and in which 95% confidence intervals of the mean at each point of the distribution are indicated. The hold-times and TOTs from different drug sessions were then combined to form a single distribution representing each dose. The use of 95% confidence intervals for control sessions enabled graphical comparison of the various distributions but visual impressions were confirmed with more rigorous statistical comparisons. The control distributions were compared with those following ethanol by the Kolmogorov-Smirnov two-sample test. Visual inspection did not reveal any consistent trends such as might be expected if tolerance develops through the course of the experiment.

Results

Figure 2 shows the hold-time and TOT distribution for SM831 and illustrates the response pattern typical for the other two monkeys. Two sharp peaks appear in the TOT distribution, one at 8.5 seconds and one at 10 seconds. The peak at 8.5 seconds (including hold-times of 8.25 to 8.75 seconds) shows that about 35% of the time spent holding the bar was spent in this band. This class interval represents occasions when the monkey released the bar or moved it out of range at the beginning of the reinforcement cycle, which began at 8 seconds. Juice delivery began at 9 seconds for half of the completed responses, so the second peak, centered at 10 seconds, represents occasions when the monkey released the bar or exited the range after receiving juice. A small peak appears at 17.25 seconds, representing occasions when the monkey held the bar for two successive responses. The last bin represents occasions when the monkey held the bar for more than two successive responses.

The overall shape of the hold-time distribution resembles that of the TOT distribution with one important exception. A much greater proportion of hold-times were less than about 2 seconds in duration. The shortest class

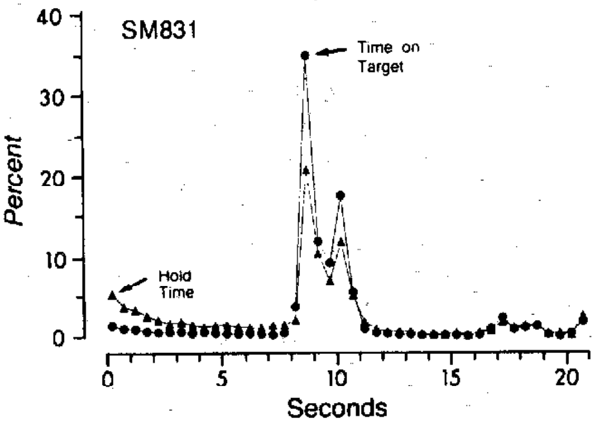

FIGURE 2. Typical dwell time distributions illustrating the time during a session spent holding the bar and the time on target for SM831. The distribution is in 0.5 second-wide bins beginning at 0.25 seconds. The dwell time in a particular class interval is obtained by multiplying the number of bar-holds (or TOTs) falling in that interval by the duration represented by the interval. This procedure weights the distribution by the duration of the event and shows the amount (or percent) of time spent in each class interval. Normalizing was achieved by dividing by the total time spent holding the bar.

interval incorporated about three times as many dwells in the hold-time distribution as it did in the TOT distribution. These short-duration holds represent occasions on which the monkey grabbed the bar and released it very quickly. The short bar-grabs appear to represent a different class of behavior than the longer ones: they were not under precise control of the reinforcement contingencies and they were not in range. Informal observations revealed that they represented either erratic, waving motions or short touches that were followed by effective responses. The smaller proportion of hold-times appearing between 8 and 10 seconds results from the greater proportion of short hold-times.

The effects of 0.5 and 1.0 gram/kg of ethanol on hold durations and time-on-target are illustrated in Figure 3. Cumulative distributions are presented because they enable uncluttered comparisons among groups. Inspection of the control and vehicle distributions show that the distributions from all three animals are similar. The sharp peaks that appear in the raw distribution (Figure 2) appear as a steep slope in the cumulated distribution (compare SM831 in the bottom panels of Figure 3 with Figure 2). During control sessions, 70% to 80% of the time holding the bar was spent in hold durations that met or exceeded the 8-second criterion and only 5% to 10% were less than 3 seconds. Ethanol produced a two- to four-fold increase in the short-duration holds for SM832 and SM834 but had little effect on them for SM831.

The essential features of responding remained intact at doses up to and including 1 gram/kg; response classes that met the criterion of 8 seconds or greater accounted for more than 50% of the time spent holding the bar for all three monkeys. More important, the shape of the TOT distribution was not profoundly affected by ethanol, indicating that ethanol's effects were predominantly on the short, erratic grabs.

Figure 4 shows representative 5.12-second samples taken from a control session and an ethanol session. During the control session, peak-to-peak excursions in acceleration ranged to almost 400 milli-g^1 (where g is the acceleration due to gravity). A dose of 1 gram/kg of ethanol produced about a 10-fold reduction in the amplitude of these excursions. The tracings in Figure 4 offer a simple way of visualizing the effect of ethanol on tremor, but provide only minimal quantification and no dose-effect information.

Figure 5 decomposes movement into different frequency bands and provides more precise, frequency-specific information about ethanol's effect on tremor. The spectra taken from control sessions contained peaks at about 8, 10.5 and 8.5 Hz for monkeys SM834, SM832 and SM831, respectively. Monkeys SM832 and SM831 also showed peaks at 16.5 and 24.5 Hz, respectively, and the higher-frequency peak was the dominant one during control sessions for SM831.

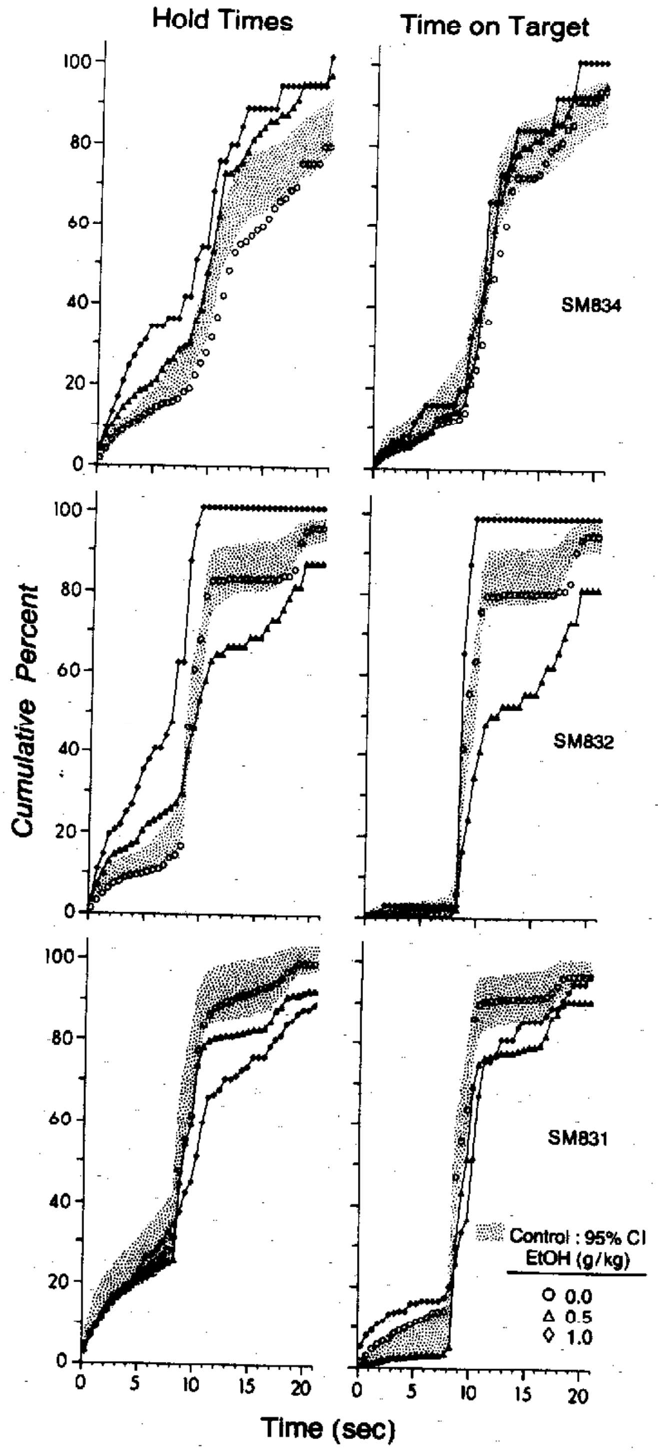

FIGURE 3. Cumulative dwell time distributions describing the hold-times (left) and time on target (right) for control (shaded) and vehicle (unfilled circles), and two doses of ethanol for all three monkeys. Ethanol increased the proportion of short-duration holds for SM834 and SM832 but had little effect on the TOTs for these monkeys. Ethanol increased the percentage of short-duration TOTs for SM831 at 1 gram/kg. Even at 1 gram/kg, a large proportion of the holds and TOTs were within the 7 to 9 second bin required by the reinforcement schedule.

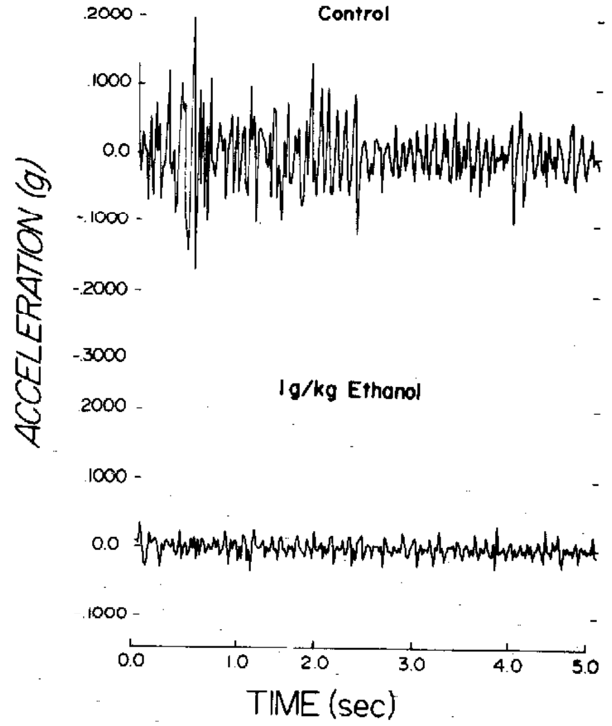

FIGURE 4. Representative 5.12 second samples from control and ethanol conditions for SM834. These are the second derivative of the position as obtained directly from the RVDT and are filtered as described in the text. The ordinates are in g's (the acceleration due to gravity) and were obtained by dividing the second derivative of displacement (measured as arc length) by 981 cm/sec^2, the acceleration due to gravity. Differentiation emphasizes frequencies of interest and facilitates comparisons with the literature. Slow undulations, while still present in these data, are de-emphasized. Ethanol reduced the peak-to-peak excursions in acceleration.

Spectra taken from vehicle sessions were statistically indistinguishable from those taken from control sessions for SM834 and SM832. The vehicle spectrum for SM831 was a different shape than the control spectrum: it peaked at about 7 Hz and may reflect stress induced by the intubation procedure.

Ethanol intubation produced dose-dependent decreases in the amplitudes of the power spectra. At doses of less than 1 gram/kg, the reduction in amplitude was not specific to any frequency band but rather appeared across all frequencies. At 1 gram/kg, the shape of the spectrum was less peaked than during vehicle or control sessions, indicating that at this dose, suppression of the dominant 6–10 Hz peak by ethanol may have been greater than that seen in other bands. Response rates were too low after a dose of 1.5 grams/kg to allow for a stable spectral estimate. Control performance was restored on the day after ethanol intubation. Even at the highest dose studied, 1.5 gram/kg, no enhanced or reduced tremor was observed 24 hours later (data not shown).

Discussion

The frequency of tremor reported in the present study was similar to that seen in normal human postural tremor, although its magnitude was lower. A dominant peak appeared at 6 to 8 Hz and its magnitude varied from 25 to 150 (milli-g)^2/Hz. Two animals even displayed a bimodal spectrum, and the location of the high-frequency modes was similar to that associated with normal human tremor (Randall and Stiles, 1964; Stiles and Randall, 1967).

The magnitude of the spectral mode and the magnitude of tremor in general are highly variable both within and across individuals (Marsden et al., 1969). In humans, the 6-8 Hz peak typically has a power of about 13 to 31 milli-g/Hz or about 180 to 1,000 (milli-g)^2/Hz (Newland, 1988; Wade et al., 1982; Wyatt, 1968). The amplitude of tremor is affected by the applied force, by fatigue or by pharmacological treatments. Tremor induced by ethanol withdrawal or by anxiogenic compounds usually contains the same modes as normal tremor but of different amplitudes. The amplitude of tremor associated with ethanol withdrawal in humans is lowered by propranolol but the frequency is unaffected (Zilm et al., 1979).

In the present study, ethanol reduced tremor in a dose-dependent manner in all three animals studied. Spectral analytic techniques provided quantitative support for previous observations that, at moderate doses, ethanol's reduction in tremor is not specific to a band of frequencies but rather extends across the entire band of frequencies. At 1 gram/kg, the tremor spectrum was flattened, an effect that suggests a proportionally larger decrease in the 8-10 Hz band, since that band dominated during vehicle sessions.

Alterations by ethanol in quantitative measures of response topography and duration have been noted in such diverse tasks as rats pressing a force lever (Samson and Falk, 1974) and dogs pressing a panel (Weiss and Laties, 1964). In the present study ethanol altered the positioning task at approximately the same doses that affected tremor, although the effect on TOT and duration was neither as dramatic nor as consistent as ethanol's effect on tremor. At doses up to and including 1 gram/kg, the fundamental features of performance remained intact; the TOT distribution and, to a lesser extent, the hold-time distribution, remained sharply peaked at the response criterion. The most consistent effect on topography was the two- to three-fold increase in the number of short-duration holds for SM834 and SM832. This increase replicated an earlier report that ethanol increases the proportion of short-duration responses in dogs trained to press a panel to accumulate a specified total duration (Weiss and Laties, 1964). Such an effect may also be consistent with chlordiazepoxide's effects on motor function in rats in a force-level paradigm: this drug reduces the number of reinforcers obtained while leaving unaltered the total time-on-task, an effect that could result from an increase in short-duration holds (Fowler et al., 1977).

In the present study, no alteration in tremor was observed 24 hours after ethanol administration. However, enhanced tremor or other motor effects might appear with a different dosing protocol or at different times after alcohol intubation (Samson and Falk, 1974; Tang and Falk, 1979). Tremor is one of the cardinal signs of ethanol withdrawal and it even has been reported on occasion in patients several hours after acute ethanol administration (Koller and Biary, 1984). Withdrawal tremor is usually characterized as a postural tremor (Koller et al., 1985; Zilm et al., 1979) because it is the same frequency as postural tremor, but 5 to 20 times the amplitude. It resembles essential tremor in that it can be reduced in magnitude by ethanol and propranolol but is reported to be characterized by a higher dominant frequency than essential tremor (Koller et al., 1985).

Ethanol's reduction of the magnitude of tremor could be related to, and may even be partially responsible for, ethanol's other motor slowing effects. Although the functions of tremor are still debated, one function seems to be that of facilitating movement. The rate of tremor has been said to be related to the highest speed with which a limb can move (Freund et al., 1984). Tremor may also facilitate movement by providing an initial direction and velocity. Ethanol's reduction of the magnitude of tremor might be reflected in the speed of movement as well as the latency to initiate movement. Both of these aspects of motor function are related to the functional consequences of tremor and they both are powerfully affected by ethanol in a variety of motor systems (Goldstein, 1983; Wallgren and Barry, 1970) including oculomotor systems (Ando et al., 1987; Katoh, 1988).

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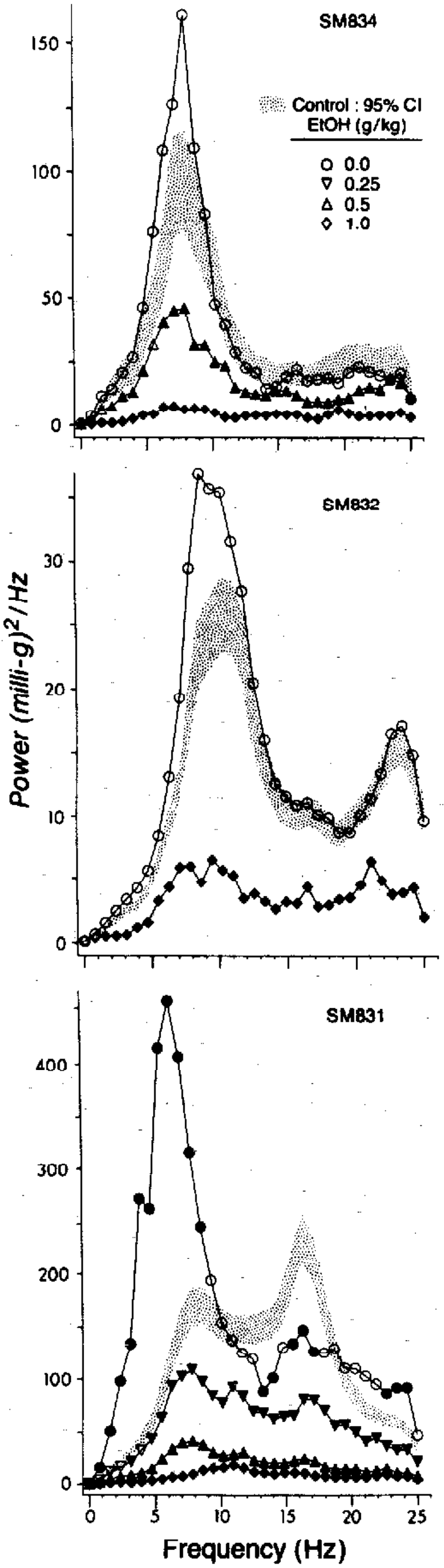

FIGURE 5 (*at left*). Spectral analysis of the second derivative of bar position obtained after control, vehicle and ethanol doses that differ from control. Confidence intervals of 95% for the geometric mean of the control sessions are represented by the shaded areas. Symbols represent the geometric mean of the spectral estimate from vehicle sessions. A symbol is filled if (1) the spectrum is different in shape from control conditions and (2) if the 95% confidence intervals do not overlap. Only ethanol doses that differed from control conditions are shown.

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