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7. Wilcoxon matched-pairs signed-ranks test; for 1979–1980, $P < .001$ and for 1980–1981, $P < .005$.
8. Spearman rank correlations (r) for the 3 years: 1979, $N = 11$, $r = 0.51$, $.10 > P > .05$; 1980, $N = 18$, $r = 0.50$, $.05 > P > .01$; and 1981, $N = 18$, $r = .03$, not significant. Sampling effort was increased after 1979 data showed interesting patterns. Statistical significance of the correlations reflects this change in effort from 1979 to 1980. Rank estimates of density used in all correlations were made in 1977. The declining correlation coefficient illustrates a more rapid change in sex ratio on trees with low density and low male frequency. The 1980 frequency of males is inversely correlated with the 1980–1981 increase of sex ratio on each tree ($r = .48$, $0.05 > P > .01$). Weather affects the survival of scale crawlers and produces variations in density that are independent of selection and host adaptation. All pines in the study area carried low insect densities in 1980 in comparison with 1979 and 1981. The consistently increasing frequencies of males indicate that density alone is not a major determinant of the sex ratio patterns.
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Early Morning Insomnia with Rapidly Eliminated Benzodiazepines

Abstract. *Early morning insomnia, a significant increase in wakefulness during the final hours of drug nights, occurred after 1 or 2 weeks of nightly administration of benzodiazepine hypnotics with short elimination half-lives, when tolerance had begun to develop. Early morning insomnia may be a variant of rebound insomnia and therefore specific to benzodiazepines, or it may occur with any rapidly eliminated sedative-hypnotic agent.*

Benzodiazepine hypnotics with relatively short elimination half-lives have recently received considerable attention, since, compared with long half-life benzodiazepine hypnotics, the short half-life drugs have little accumulation and potentially produce less daytime sleepiness and smaller performance decrements (*1*). As with any drug, however, benzodiazepine hypnotics with relatively rapid elimination rates cannot be uncritically accepted with the assumption that their administration or withdrawal is entirely without undesirable effects. In fact, these drugs produce rebound insomnia, an intense worsening of sleep relative to baseline levels, after they are withdrawn (*2*). This adverse effect occurs even when these drugs are administered in only a single nightly dose for short periods. We now describe a new finding of early morning insomnia that is similarly associated with benzodiazepines having relatively short elimination half-lives. This condition also consists of a worsening of sleep, but it occurs during the final hours of sleep during actual drug administration, whereas rebound insomnia occurs after drug withdrawal. Both phenomena can be interpreted as manifestations of drug withdrawal.

We now present data analyzed from six separate sleep laboratory evaluations of four benzodiazepine hypnotic drugs (*3*). The subjects, whose primary complaint was of chronic insomnia, were continuously monitored by hypnopolygraphic recordings consisting of an electroencephalogram, electromyogram, and electrooculogram (*4*). On every night of these studies each subject received either drug or placebo at "lights out," and then was monitored for an 8-hour period. Throughout the study the subjects were instructed not to nap, not to alter their level of daily physical activity significantly, and not to use any drugs or alcohol.

Two benzodiazepines with short elimination half-lives (*5*) were evaluated: midazolam (20 mg) ($N = 6$) in a 14-night study that included four placebo nights (the first for adaptation and the next three for baseline measurements), 1 week of drug administration, and three placebo-withdrawal nights; and triazolam (0.5 mg) ($N = 7$) in a 22-night study that included four placebo-baseline nights, 2 weeks of drug administration, and four placebo-withdrawal nights (*3*). Two benzodiazepines with long elimination half-lives (*6*), flurazepam (30 mg) and quazepam (30 mg), were also evaluated. For flurazepam, a total of 15 subjects were assessed in three studies, 4 in a 22-night study identical to that described for triazolam and 11 in two separate 47-night studies that included four placebo-baseline nights, 4 weeks of drug administration (for this report, data were analyzed for only the first 2 weeks of drug administration), and 15 placebo withdrawal nights. For quazepam, six subjects were studied in a 47-night study identical to that used for flurazepam (*3*).

For each drug, data were analyzed for two sets of three consecutive drug nights by comparing each of their mean values with the mean value of the set of three baseline nights [Dunn multiple-comparison, two-tailed t-test (*7*)]. For the midazolam study, the first three drug nights (nights 5 to 7) and the last three drug nights (9 to 11) of a 1-week drug administration period were used. With the other three drugs, data were also analyzed from the first three drug nights (5 to 7) and the next available set of three drug nights recorded in the sleep laboratory (nights 16 to 18), which represented the last three drug nights of a 2-week drug administration period. (Because of the design of these studies, sleep laboratory data were not obtained on nights 9 to 11 as they were in the midazolam study.)

All four drugs decreased the time spent awake during the first 6 hours of the night on each of the two sets of three consecutive drug nights. This effect was variable across drugs for the last 2 hours of these drug nights, however. On nights 5 to 7, midazolam decreased mean wake time 37.5 percent below baseline for the first 6 hours (from 47.5 ± 5.5 to 29.7 ± 3.1 minutes, $P < .01$), but during the last 2 hours, only 7.4 percent [from 13.5 ± 4.6 to 12.5 ± 3.2 minutes, not significant (N.S.)]. Triazolam had a similar effect, decreasing wake time 46.6 percent for the first 6 hours (from 84.8 ± 9.2 to 45.3 ± 3.4 minutes, $P < .01$) but only 27.7 percent (from 8.3 ± 1.2 to 6.0 ± 0.9 minutes, N.S.) during the final 2 hours. In contrast, both quazepam and flurazepam were effective in maintaining sleep throughout the

Table 1. Early morning insomnia rate. Mean percentage (± standard error) of subject nights on which wake time during the last 2 hours was significantly greater ($P < .05$) than during baseline nights (*8*).

Drug	*N*	Nights 5 to 7 (%)	Nights 9 to 11 or 16 to 18 (%)	All drug nights (%)
Short half-life				
Midazolam (20 mg)	6	27.8 ± 13.4*	55.6 ± 7.0*	41.7 ± 9.4*
Triazolam (0.5 mg)	7	9.5 ± 6.1	38.1 ± 8.7*	23.8 ± 6.1*
Long half-life				
Flurazepam (30 mg)	15	6.7 ± 3.6	11.1 ± 5.3	8.9 ± 3.6
Quazepam (30 mg)	6	5.6 ± 5.6	5.6 ± 5.6	5.6 ± 3.5
Combined rate		6.3 ± 2.9	9.5 ± 2.1	7.9 ± 2.7

*Significantly different ($P < .01$) from the combined rate for long half-life drugs.

night. Quazepam decreased wake time in the first 6 hours by 55.6 percent (from 55.7 ± 9.6 to 24.7 ± 2.7 minutes, $P < .01$) and in the last 2 hours by 69.9 percent (from 14.3 ± 3.9 to 4.3 ± 1.0 minutes, $P < .05$). Flurazepam decreased wake time by 47.5 percent during the first 6 hours (from 68.4 ± 6.4 to 35.9 ± 3.7 minutes, $P < .01$) and by 60.3 percent during the last 2 hours (from 15.1 ± 2.4 to 6.0 ± 1.5 minutes, $P < .01$).

During the next drug administration period evaluated, early morning insomnia occurred with the two short half-life benzodiazepines. Midazolam produced the most dramatic effect, reducing wake time during the first 6 hours of the night by 32.8 percent (from 47.5 ± 5.5 to 31.9 ± 3.2 minutes, $P < .01$), but then increasing wake time by 103.0 percent in the last 2 hours (from 13.5 ± 4.6 to 27.4 ± 5.9 minutes, $P < .05$). Triazolam decreased wake time by 24.6 percent in the first 6 hours (from 84.8 ± 9.2 to 63.9 ± 5.0 minutes, $P < .01$) but by the last 2 hours had lost effectiveness; the increase in wake time (from 8.3 ± 1.2 to 13.5 ± 3.3 minutes) was not significant. In contrast, on nights 16 to 18, both quazepam and flurazepam maintained effectiveness throughout the night. Flurazepam decreased wake time by 50.6 percent for the first 6 hours (from 68.4 ± 6.4 to 33.8 ± 2.9 minutes, $P < .01$) and by 43.7 percent for the last 2 hours (from 15.1 ± 2.4 to 8.5 ± 1.4 minutes, $P < .05$). For quazepam the values for wake time for the first 6 hours were 55.7 ± 9.6 minutes on baseline and 40.9 ± 5.8 minutes on drug (N.S.) and for the last 2 hours, were 14.3 ± 3.9 minutes on baseline and 7.3 ± 1.8 minutes on drug (N.S.).

When we evaluated the second set of three drug nights for each of the four drugs on a night-by-night basis, we observed that all six values of wake time during the last 2 hours of the night for the two short half-life benzodiazepines were above baseline and all six values for the two long half-life benzodiazepines were below baseline (sign test, $P < .02$). Thus, with midazolam, wake time during the last 2 hours for nights 9, 10, and 11 increased from 13.5 ± 4.6 minutes to 38.4 ± 12.4 ($P < .01$), 26.6 ± 10.9 (N.S.), and 17.2 ± 4.8 (N.S.) minutes, respectively. A similar increase was observed with triazolam for nights 16, 17, and 18: from 8.3 ± 1.2 minutes to 12.9 ± 7.7 (N.S.), 18.1 ± 6.1 ($P < .01$), and 9.5 ± 2.8 (N.S.) minutes, respectively.

To further investigate the condition of early morning insomnia, we estimated the rate of its occurrence. For each of the six nights of drug administration for each of the four drugs, we determined the total number of times that each subject's wake time during the last 2 hours of the night significantly exceeded baseline values (*8*). In each set of three consecutive drug nights, a mean rate for early morning insomnia was obtained by calculating the percentage of subject nights exceeding baseline (Table 1). The Dunn multiple-comparison, two-tailed *t*-test (*7*) was used to compare the early morning insomnia rate for each of the short half-life drugs with the combined rate of the two long half-life drugs. (The data for quazepam and flurazepam were combined since they did not differ from each other on either set of drug nights.)

On the first three drug nights, midazolam had an early-morning insomnia rate during the last 2 hours of the night significantly greater than the composite rate for quazepam and flurazepam ($P < .01$) (Table 1). During the final three drug nights, the early morning insomnia rates for the two short half-life benzodiazepines were each significantly greater than the composite rate for the long half-life drugs ($P < .01$).

For those nights on which early morning insomnia occurred, the average increase in wake time and the total amount of time spent awake (both values in minutes) during the last 2 hours of the night were: for midazolam, 30.3 ± 9.4 and 44.7 ± 12.6; for triazolam, 23.1 ± 5.8 and 35.8 ± 6.5; for flurazepam, 7.8 ± 5.1 and 14.9 ± 7.7; and for quazepam, 7.3 and 10.8 ($N = 1$).

These findings indicate that the rate at which a drug is eliminated from the body is critical in determining whether early-morning insomnia occurs. We previously demonstrated that the occurrence of rebound insomnia following withdrawal of a drug also depended on its elimination time (*2*). Thus, drugs rapidly eliminated produce the most frequent and intense worsening of sleep—either rebound insomnia or early morning insomnia; these syndromes are either not present or, if so, only minimally with benzodiazepines that are eliminated slowly.

Throughout each of the studies discussed here, subjects also provided estimates of their tension or anxiety levels during the daytime on a seven-point scale. For purposes of comparison, these values were transformed to *z* scores relative to each subject's own baseline. During the week of midazolam administration and the second week of triazolam administration, tension or anxiety increased above baseline and differed significantly from the values for the same week for the two long half-life drugs (midazolam, 0.79 ± 0.37 versus −1.12 ± 0.58, *t*-tests, $P < .05$; triazolam, 0.94 ± 0.67 versus −0.80 ± 0.41, $P < .05$). This finding of daytime rebound anxiety during the administration period of short elimination half-life drugs is consistent with our previous speculation (*2*) and with the recent finding of an increase in daytime anxiety during the administration of triazolam (*9*).

Previously we speculated that abrupt withdrawal of rapidly eliminated benzodiazepines may result in intense rebound insomnia because of a lag in production of endogenous benzodiazepine-like compounds (*2*). More recently, Snyder has proposed a similar hypothesis involving γ-aminobutyric acid mechanisms (*10*). The hypothesis proposed for explaining the mechanism of rebound insomnia can be extended to early morning insomnia, since they seem closely related. Early morning insomnia can be viewed as a variant of rebound insomnia occurring during an actual drug night.

In addition to a drug's rate of elimination, its dose and length of administration, its absorption and distribution characteristics, and the rapidity with which tolerance develops, should be important considerations in determining its potential for rebound insomnia and consequently for early morning insomnia. Also, changes in the number of benzodiazepine receptors in response to previous drug administration, the affinity of the receptor for a given drug, and the

possibility that benzodiazepines may selectively attach to subclasses of benzodiazepine receptors must be considered (*11*).

Early morning insomnia may not be unique to benzodiazepines, as rebound insomnia is (*2*); it may also occur with other sedative agents such as nonbenzodiazepine hypnotics with relatively rapid rates of elimination. Alcohol, which is known for its sedative properties and its short elimination half-life, also increases wakefulness during the second half of the night (*12*).

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Shadows of Thought: Shifting Lateralization of Human Brain Electrical Patterns During Brief Visuomotor Task

Abstract. *Dynamic spatial patterns of correlation of electrical potentials recorded from the human brain were shown in diagrams generated by mathematical pattern recognition. The patterns for "move" and "no-move" variants of a brief visuospatial task were compared. In the interval spanning the P300 peak of the evoked potential, higher correlations of the right parietal electrode with occipital and central electrodes distinguished the no-move task from the move task. In the next interval, spanning the readiness potential in the move task, higher correlations of the left central electrode with occipital and frontal electrodes characterized the move task. These results conform to neuropsychological expectations of localized processing and their temporal sequence. The rapid change in the side and site of localized processes may account for conflicting reports of lateralization in studies which lacked adequate spatial and temporal resolution.*

Many investigators have reported that brain activity is lateralized during cognitive tasks. Advanced radiological methods reveal relative localization and lateralization, but cannot resolve temporal sequencing because of the long time required for observation. Studies of ongoing, background electrical activity do not reveal split-second changes in neurocognitive patterns, and those that have reported lateralization of neurocognitive activity have been questioned on methodological grounds (*1–6*). Although the components of averaged event-related potentials (ERP's) may indicate the sequencing of some neurocognitive processes, they have not revealed consistent, robust signs of lateralization, even for language (*7*). Conclusions derived from patients with focal brain lesions or with "split-brains," cannot be directly extended to normal subjects. Lateralized processes inferred from reaction time differences to hemifield or dichotic stimulation have also been questioned on methodological grounds (*8*). These factors have undoubtedly contributed to conflicting reports of lateralization of brain activity.

To observe the spatial patterns and sequencing of neurocognitive activity, we have developed a new method called neurocognitive pattern (NCP) analysis. In NCP analysis the average ERP's of each person are used to determine the time intervals of task-related neural processes. Within these intervals the similarity of brain-potential waveshapes over the scalp is measured on a single-trial basis by computing the cross-correlation coefficient between paired combinations of electrodes. Although the neuroanatomic origin and neurophysiological significance of these correlations is not known, it has been suggested that cognitive activity may be associated with characteristic scalp correlation patterns (*9*). However, task-related electrical signals from the brain are spatially smeared in transmission to the scalp and are embedded in background activity. Since linear statistical methods were not effective in dealing with these obstacles, we used a more powerful analysis called trainable classification-network mathematical pattern recognition (*2, 3, 10–13*). For this method, artificial intelligence algorithms are used to extract patterns of correlation that differ between two conditions with no assumptions about the distribution of correlation values. The algorithm is first applied to a labeled subset of the experimental data called the training set, and the invariant patterns (classification functions) found are then verified on a separate unlabeled subset of data called the test set. If the classification functions can significantly separate the test set into the two conditions, the extracted patterns have intrinsic validity.

Previously we reported the existence of complex, rapidly changing patterns of brain-potential correlation involving many areas of both hemispheres that distinguished numeric and spatial judgments in a visuomotor task (*13*). Since the sequencing of neurocognitive differences between numeric and spatial processing is not definitely known, the complex patterns were difficult to interpret. The present experiment was designed to clarify this situation by highlighting presumably localized neural processes. In comparing two types of spatial judgment, the common activity of brain areas should cancel, revealing differences in the right parietal area presumed to mediate spatial judgments. The right-handed finger response in one task was designed to elicit lateralized activity of the left central motor area.