Pharmacology Biochemistry & Behavior, Vol 29, pp 517–523 © Pergamon Press plc, 1988 Printed in the U S A 0091-3057/88 $3 00 + 00

Amphetamine Accelerates and Attenuates Ultradian Activity Rhythms in Preweanling Rats

MARTIN H. TEICHER,[1] NATACHA I. BARBER,
ROSS J. BALDESSARINI AND BENNETT A. SHAYWITZ*

Departments of Psychiatry and Neuroscience Program, Harvard Medical School
Mailman Research Center, McLean Hospital, Belmont, MA 02178
*and *Laboratory of Developmental Neurobiology, Department of Pediatrics and Neurology*
Yale University School of Medicine, New Haven, CT

Received 1 December 1986

TEICHER, M H , N I BARBER, R J BALDESSARINI AND B A SHAYWITZ *Amphetamine accelerates and attenuates ultradian activity rhythms in preweanling rats* PHARMACOL BIOCHEM BEHAV **29**(3) 517–523, 1988 — Developing rats, studied in environmental isolation, display prominent fluctuations in locomotor activity with a periodicity of about 1–3 hr This ultradian rhythmic pattern is most marked at 2 weeks of age, and appears to be endogenously mediated (+)Amphetamine (1 mg/kg) was administered to 2 week old rat pups, and their locomotor activity levels were recorded continuously and stored in 5 min intervals using a sensitive computer-interfaced vibrational activity monitor Activity was recorded for 12 hr after treatment and resulting time-series data were analyzed by harmonic spectral techniques During the first 6 hr of testing, amphetamine induced a prominent low frequency perturbation in baseline activity levels corresponding to the expected period of acute drug action During this time, normally prominent ultradian activity rhythms in the range of 8–12 cycles per day (cpd) were diminished in amplitude, even following low frequency smoothing to remove the changes in baseline Correspondingly, there was also an increase in ultradian rhythm amplitude in amphetamine-treated pups at higher frequencies (32–40 cpd) During the final 6 hr of testing there was a marked suppression of typical ultradian rhythms in amphetamine-treated pups but not in controls These results suggest that amphetamine treatment both accelerates and attenuates ultradian activity rhythms in developing rats during the acute period of drug action, and produces a prominent diminution in these rhythms during subsequent rebound and recovery periods

Amphetamine Ultradian Locomotion Biological rhythms Development Chronobiology

ACTIVITY rhythms with a 1–2 hr periodicity were first recognized in rats by Richter [22], who explored their early ontogeny [23] Kleitman [13] also discerned a prominent 1–2 hr fluctuation in activity of human newborns, and hypothesized a basic rest-activity cycle during the waking state, similar to the rapid eye movement (REM) cycle observed during sleep, and possibly due to similar neural mechanisms From these historic origins have emerged a substantial body of literature demonstrating ultradian (>1 cycle per day) fluctuations in many physiological processes (e g , [16]) Such rhythms appear to provide a ubiquitous undercurrent throughout the animal kingdom [7], and have even been observed in isolated enzyme systems [4]. Most evidence suggests that these phenomena are likely to reflect the effects of multiple independent oscillators, and direct linkage between such rhythms as the REM sleep cycle and waking ultradian activity rhythm probably does not occur [16]

Ultradian rhythms differ markedly from more extensively studied circadian cycles, in that they appear to lack a consistent "zeitgeber" to impose an external cadence. Thus, little synchronicity is generally found between subjects, who appear to "free-run" at independent and variable frequencies Moreover, commonly observed ultradian rhythms (e.g., activity, REM sleep, cortisol secretion) display prominent circadian variations in amplitude, and possibly also in ultradian frequency [14] This modulation results in special problems in the identification and analysis of such rhythms, and has severely limited attempts to probe their neurobiological underpinnings In recent years, considerable progress has been made toward understanding the functional neuroanatomy and pharmacology of central nervous system (CNS) oscillators responsible for REM sleep [17], and neuroendocrinologists are beginning to outline the control processes responsible for pulsatile hormone secretions [18]

We have undertaken a series of investigations on the effects of psychotropic agents on this basic rest-activity rhythm. There were two complementary reasons for these studies First, virtually nothing is known about the neural

[1]Requests for reprints should be addressed to Dr Martin H Teicher, Mailman Research Center, McLean Hospital, 115 Mill Street, Belmont, MA 02178

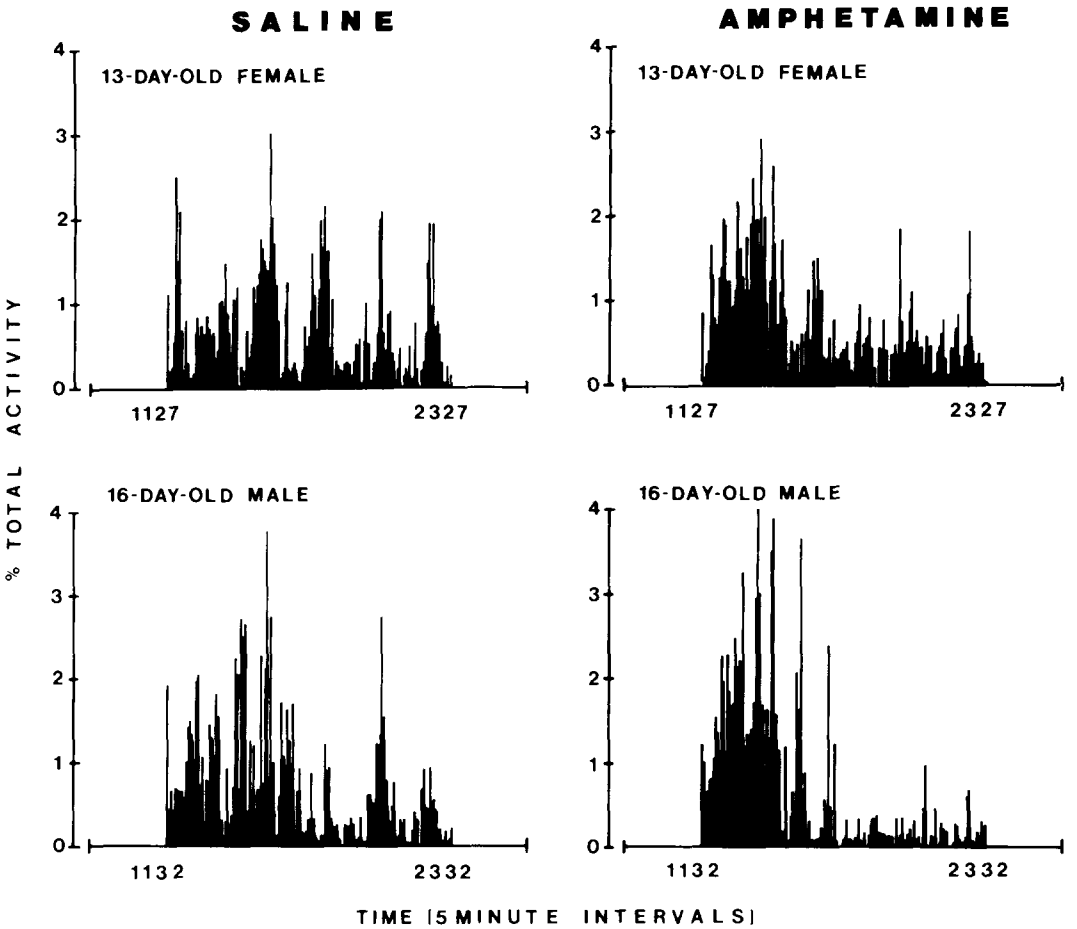

FIG 1 Activity profiles of isolated littermate pairs at 13 and 16 days of age which had received injections of saline or (+)amphetamine Activity was measured with a computer-interfaced vibrational activity monitor and is expressed as percentage of total activity per 5 minute epoch Activity was monitored for twelve continuous hours

systems producing this rhythm, and pharmacological agents can serve as useful probes to help identify neurotransmitter systems involved in its temporal maintenance Second, there are emerging data from animal model and clinical studies suggesting that disturbances in ultradian rhythms may occur in some neuropsychiatric disorders—such as depression [2, 15, 28], dementia [31], and childhood hyperactivity [5]—and knowledge of how drugs affect these rhythms could be of clinical value

In order to explore the neuropharmacology of ultradian activity rhythms, we have selected for study the developing albino rat, as it displays prominent fluctuations in activity with about the same periodicity as humans [28,29], and because much is known about the neuropharmacology of the rat In the present study, we concentrated on the two-week old rat, which, like newborns of many species, displays prominent ultradian fluctuations in motility [29]

Studies designed to assess the effects of drugs on ultradian motility cycles in rodents have been rare In two brief reports, del Pozo *et al* [8,9] examined the effects of (+)amphetamine (2 mg/kg, IP) on ultradian activity rhythms of isolated and aggregated *adult* mice They found that amphetamine had a greater effect on isolated mice, in which it appeared to produce a shift in the main peak period of the ultradian rhythm from 187 min (7 7 cycles per day [cpd]) to 250 min (5 8 cpd), and to decrease the prominence of a minor secondary peak at 93 min (15 5 cpd) The present study was conducted to see if these observations could be extended to developing rats with more prominent ultradian activity rhythms than adult rodents Care was taken to separate effects of amphetamine on baseline activity from its effects on the usually prominent ultradian activity surges, and to distinguish between the effects of amphetamine during the period of acute drug action (ca 6 hr in the neonate [6]), from possible effects during rebound and recovery

METHOD

Subjects

Male and female Sprague-Dawley rat pups were reared in natural litters culled to 10 pups each on day 2 Multiparous mothers were shipped from Charles River Breeding Colony on the first day after delivery Litters were housed in maternity cages with pine shavings for bedding under a 12 12 hr light/dark cycle (on 0700–1900 hr) Temperature was maintained at 25±2°C Pups were studied between 13 and 17 days of age Two littermates of the same sex were tested simultaneously One pup received saline and the other am-

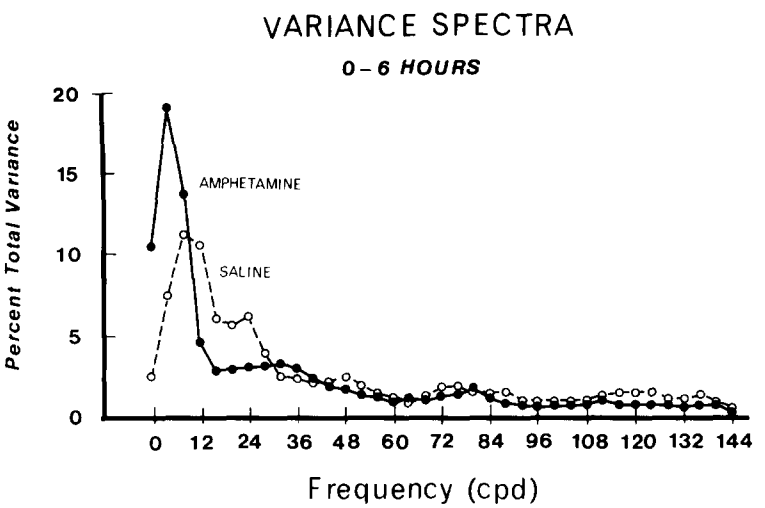

FIG 2 Spectral analysis of the first six hours of activity following the acute administration of saline or (+)amphetamine to developing rats The graph indicates the percentage of total variance in the activity time series that can be accounted for by each harmonic frequency band ranging from 0–144 cpd at 4 cpd increments Shown are group spectra derived from the individual analysis of eight littermate pairs receiving saline or amphetamine

phetamine The final subject pool consisted of 8 amphetamine treated, and 8 control pups from 4 different litters Subjects were tested only once

Test Apparatus

Activity was quantified using a four channel vibrational activity monitor similar to a previously described prototype and technique [30] A sensitive mechanical-to-electrical transducer consisted of a 25 cm diameter enclosure mounted on a 10 cm permanent magnetic speaker. Signals from the transducer were sent to a four channel linear amplifier, where they were filtered (100 Hz high frequency roll-off), and amplified 1000 times A voltage comparator circuit then compared amplified signals to a preset threshold voltage. Vibrational signals exceeding the threshold produced a digital output pulse These pulses were monitored (>1 KHz) and processed by a Rockwell AIM-65 Microcomputer with BASIC and Assembly language control programs Summated activity scores were determined at 5 min test intervals, and printed out during the 12 hr test period

The four channels were calibrated individually using a low-frequency oscillator coupled to a signal generator Threshold settings for each channel were adjusted to produce identical readings at the desired sensitivity level, which enabled the device to detect virtually all visible motions except respiration and slow head turning in representative two week old rats The same settings were used for each replication, and subjects were randomly distributed to each channel.

Procedure

On the day of testing, pups were removed from their litters, weighed, and injected intraperitoneally (IP) with either (+)amphetamine sulfate (1 mg of the salt/kg) or sterile isotonic saline in an injection volume of 0 1 ml/20 g bodyweight. Shortly after injection each pup was placed in a test cage housed in an isolation chamber maintained at 30±1°C During the test period the subjects were maintained in darkness in order to ascertain drug effects of these rhythms unconfounded by exogenous light-dark transitions

DATA ANALYSIS

Activity Conversion

Activity scores were transcribed into files for an Apple II microcomputer As we were concerned with the effects of drug on activity patterns, and not interested in absolute levels of activity, the raw activity scores were transformed into percent of total activity Data from the first 6 hr and last 6 hr were analyzed separately, using programs written for the Apple II by Teicher and Barber [26,27] Data, typically, are means±SEM

Variance Spectrum Analysis

The main technique used to analyze the data was the method of low resolution variance spectral analysis described by Blackman and Tukey [3] and by Halberg and Panofsky [10,20], and recommended by Kripke [14] as the most suitable time-series technique for the analysis of ultradian rhythms Raw variance spectra were calculated for each 6 hr series Group spectra were obtained by averaging the results of the independent spectra, and hamming (smoothing by use of a weighted moving average) the aggregate to improve the reliability of the spectral estimates [3, 10, 20]

The derived spectra contain the amount of variability (spectral variance) accounted for by each frequency band from 0 to 144 cycles per day (cpd) at 4 cpd intervals Thus, a hypothetical value of 12% in the 16 cpd bandwidth of a group of subjects would indicate that about 12% of the variability in their activity data could be accounted for by a rhythm of this frequency If no significant periodicities were present in the data, than each spectral bandwidth would contain about 2 8% of the total variance by chance. If the rhythm does not occur at one of the indicated harmonic bandwidths, the percent variance would be distributed between adjacent bandwidths (e g , a 10 cpd rhythm would have its spectral

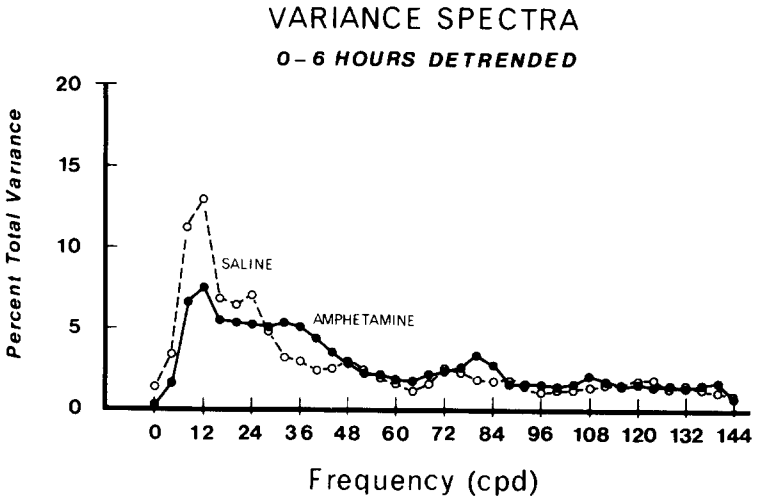

FIG 3 Spectral analysis of detrended activity data for the first six hours following the acute administration of saline or (+)amphetamine to developing rats The graph indicates the percentage of total variance in the activity time series that can be accounted for by each harmonic frequency band ranging from 0–144 cpd at 4 cpd increments Detrending was accomplished by fitting the raw activity data of each subject to a best-fit low-frequency cosine function, and then by mathematically removing this frequency The detrended data was then reanalyzed to ascertain the effects of amphetamine on ultradian rhythmicity once the effects of amphetamine on basal activity were removed (see text for further discussion)

variance distributed between 8 and 12 cpd) A very regular periodicity produces a sharp spectral peak, whereas a less-stable rhythm produces a broad peak distributed across a number of frequency bands

The accuracy of the obtained spectral estimates is affected by the number of subjects, the duration of the total test period, the number of measures obtained, and by other technical factors related to the size of the lag window and the final smoothing procedure [10,20] A valuable numerical feature of this analysis is that the accuracy of each calculated spectral point is a constant percentage of its magnitude For these analyses, each bandwidth was determined with 19 5 degrees of freedom [10], resulting in a standard error of measurement of 7 5% for each point Thus, a spectral variance result of 12% could be read as 12±0 9% (0 9= 12×7 5)

Sinusoidal Detrending

During the first 6 hr of testing, amphetamine produced a marked increase in baseline activity levels, thereby creating an artifactual sinusoidal rhythm that resulted in a biased estimate of low-frequency spectral intensity As the magnitude of this peak could diminish the spectral estimate of other peaks, a technique was required to remove this periodicity mathematically to obtain unbiased estimates of surrounding spectral periodicities [9–11, 20] The first 6 hour activity data from each animal were thus subjected to a detrending procedure in which the data were fit to a cosine function, whose amplitude, frequency, phase angle, and mesor were determined by iterative nonlinear least-squares analysis [24,27] The difference between actual activity and low-frequency cosinor fit were calculated and reconverted into a detrended activity time-series. These 'prewhitened' data files, with their low-frequency sinusoidal oscillation removed, were subjected to further analysis by the techniques described above

Group Comparisons

Statistically significant differences between the variance spectra of the two groups were determined by multiple *t*-test comparison of the spectral estimates To correct for the number of cross comparisons in each spectral series the pair-wise alpha level was adjusted to maintain an experiment-wise alpha level of 0 05 using the formula

$$alpha_{pw} = 1 - (1 - alpha_{ew})^{(1/n)},$$ where n = number of comparisons

Thus, even though 37 comparisons were made between each spectral series, the probability of obtaining any significant difference was set equal to 0 05 for the entire series

Kolmogorov-Smirnov Test

To determine whether a significant rhythm exists in the activity data, the aggregate spectral analysis was tested using the Kolmogorov-Smirnov test The spectrum of pure white noise is a flat line with a linear cumulative distribution function. The Kolmogorov-Smirnov test ascertains whether the cumulative distribution function of the calculated variance spectrum significantly departs from a theoretical white noise distribution function [25,32] Significant departure from pure white noise indicates that the time series contains periodicities of significant magnitude that would not be expected to occur by chance

RESULTS

Activity Profiles

Two-week old developing rats given saline control injections showed prominent spontaneous ultradian fluctuations in behavioral activity with a periodicity of 1–3 hr (Fig 1) (+)Amphetamine (1 mg/kg, IP) produced an acute increase in the basal activity level that peaked after about 3 hr and

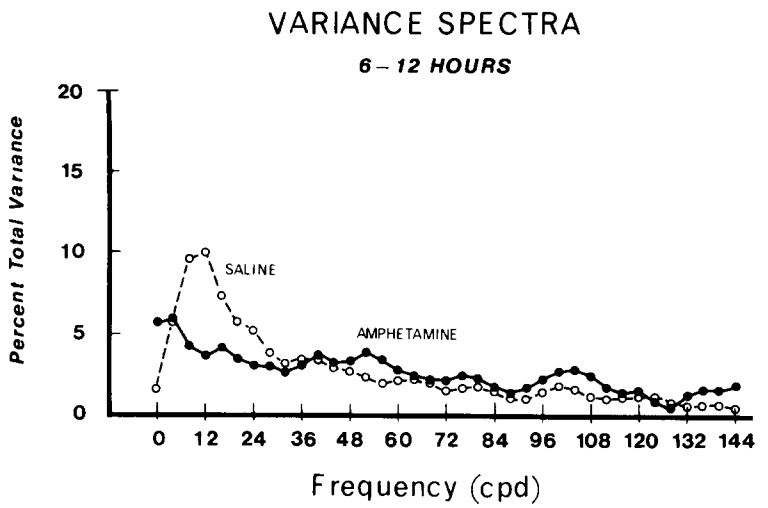

FIG 4 Spectral analysis of the hours 6–12 of activity following the acute administration of saline or (+)amphetamine to developing rats The graph indicates the percentage of total variance in the activity time series that can be accounted for by each harmonic frequency band ranging from 0–144 cpd at 4 cpd increments

then rapidly decayed Ultradian fluctuations in activity persisted during this baseline perturbation, but appeared to slow as the acute stimulatory effect of amphetamine declined, and were not apparent during the second 6 hr of testing

Spectral Analysis, 0–6 Hours

During the first 6 hr of testing saline-treated control pups displayed a prominent though fairly broad peak of activity in the slow ultradian domain, with a dominant peak between 8 and 12 cpd, extending to 28 cpd (Fig 2). Based on the raw data, the amphetamine-treated pups had an enormous ultradian "pseudo-peak" at 4 cpd, that was evidently an artifact of the acute sinusoidal perturbation of baseline activity Saline-treated pups showed a greater percentage of their spectral variance between 12 and 24 cpd than their amphetamine-treated littermates (all $p<0$ 005) However, as the results of this analysis are expressed as *percent* total variance, the large 4 cpd "pseudo-peak" could effect the magnitude estimation of other spectral components, and give the false impression that they were less prominent in treated subjects than control. Thus, the data were detrended to remove this possibly confounding artifact

Sinusoidal Detrending

The first 6 hr of locomotor activity (72 measurements) in amphetamine-treated pups were best fit by a cosine function with an amplitude of 0.72±0 07, and a frequency of 4 7±0 5 cpd. Saline-treated pups were fit by a less prominent oscillation of similar frequency (amplitude. 0.32±0 10, frequency 5 1±0 7) These sinusoidal rhythms correlated on average, r=0.61±0 04 with the raw activity data of amphetamine-treated pups, and correlated at r=0.31±0 06 in controls Removing the best-fit oscillation from each subject's activity profile, and reanalyzing, produced the variance spectra shown in Fig 3

This detrending procedure was very effective, reducing the magnitude of the 4 cpd bandwidth from 19.3% to 1 6% in amphetamine-treated rats, and from 7.6% to 3 3% in controls The saline-treated pups displayed greater spectral variance in the 8 and 12 cpd bands (all $p<0$ 02), whereas amphetamine-treated pups had greater spectral variance in the 32–40 cpd bandwidth (all $p<0$ 02) Thus, during the first 6 hr of amphetamine treatment, a prominent low-frequency pseudopeak was produced The underlying ultradian rhythm, factoring out the effect of the baseline change, was attenuated in the usual 8–12 cpd bandwidth, and accentuated in the higher, 32–40 cpd, frequency range

Spectral Analysis, 6–12 Hours

During the final 6 hr of testing, saline-treated pups displayed typical ultradian rhythms with peak frequency at 8–12 cpd (Fig 4) Amphetamine-treated pups displayed a very flat spectrum, with far less magnitude in the 8–24 cpd frequency range than controls (all $p<0$ 05) Kolmogorov-Smirnov analysis of these results (Fig 5) indicated that the variance spectra of control pups significantly departed from a theoretical white noise spectrum, and thus suggests that it contains significant rhythmicities. The variance spectrum of amphetamine-treated pups, on the other hand, did not deviate significantly from white noise, and does not enable us to reject the null hypothesis that there were no significant periodicites in their activity during hours 6–12 Thus, during the rebound and recovery phase after amphetamine treatment, characteristic ultradian rhythms are severely attenuated, and possibly eliminated

DISCUSSION

Overall, the present results suggest that acute administration of (+)amphetamine at 1 mg/kg, IP, accelerates and attenuates ultradian activity rhythms in developing rats during the period of acute drug action (0–6 hr), and severely blunts these rhythms during the subsequent recovery period (6–12 hr) These two phases may reflect changes in stores of monoamines such as dopamine, which become temporarily depleted in neonatal rats for several hours after amphetamine treatment [12]

Our greatest concern with these data centers on the difficulty entailed in distinghishing the acute effects of

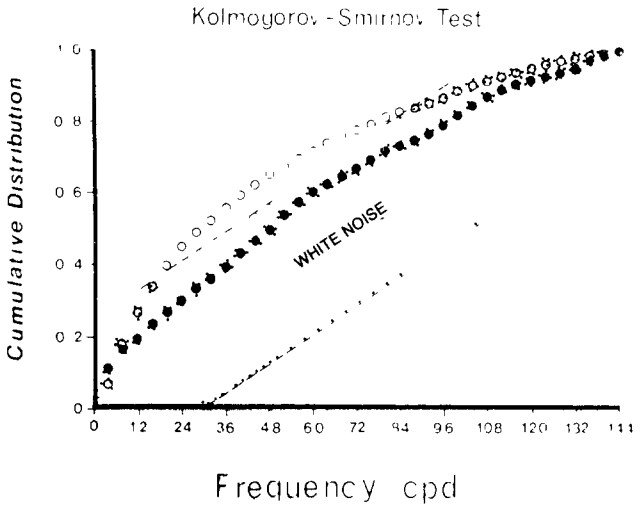

FIG 5 Kolmogorov-Smirnov analysis of group variance spectra (hours 6–12) for rat pups receiving saline (opened circles ○) or (+)amphetamine (filled circles ●) Displayed are the cumulative distribution functions for both spectra across frequency The dotted line indicates the theoretical cumulative distribution function for pure white noise (in which every frequency is equally represented), while the shaded area is the 95% confidence interval Spectra that contain significant periodicities ($p<0$ 05) depart from a pure white noise function in at least one frequency band Note that the cumulative spectra of the amphetamine-treated pups remained well inside the probability space for white noise

(+)amphetamine on ultradian rhythmicity in the face of a prominent time-dependent change in basal activity levels that appears as a large pseudoperiod on spectral analysis As discussed by Panofsky and Halberg [20] in their original description of this analytical method, "variance spectra of a time series tend to be inaccurate in regions in which the spectrum varies rapidly and extensively, as in the neighborhood of a strong peak A better spectrum can be obtained in the neighborhood of such a peak if the peak is first removed " This was accomplished using a sinusoidal detrending procedure Both the original and detrended data indicated that (+)amphetamine acutely suppressed the normally prominent 16 cpd (90 min) ultradian activity rhythm observed in rats of this age Similarly, Okamoto *et al* [19] has recently reported that (+)amphetamine completely suppressed ultradian fluctuations in hypothalamic temperature during sleep, suggesting that these observations may generalize to other ultradian rhythms We have also observed [1] that acute and continuous administration of an inhibitor of neuronal uptake of norepinephrine, desipramine, suppresses ultradian rhythmicity as well, suggesting that this observation may be applicable to other agents that affect catecholamine systems

These results complement the findings of del Pozo *et al* [8,9], who reported the emergence of a prominent slow ultradian cycle (5 8 cpd), and attenuation and possible acceleration of a secondary ultradian peak (15 5 cpd) after administration of (+)amphetamine (2 mg/kg, IP) to adult mice The very slow cycle which they reported may have been due to a sinusoidal perturbation of baseline activity that was not fully removed by their low-frequency filtering technique Shifts in their secondary peak may correspond to our observation of attenuation and acceleration of the dominant ultradian rhythm (Figs 2–4), although del Pozo *et al* [8,9] pooled data from over an entire 24 hr test period, and did not separate phases of acute drug action from those of later rebound and recovery By combining data obtained during an early phase of intense aminergic stimulation and subsequent phase of relative aminergic deficit [12], their findings may not accurately reflect the differential effects of the drug A separation of early and late phases of drug action may help clarify the chronobiological effects of agents such as amphetamine, with a relatively short behavioral half-life and multiple, time-dependent effects

More generally, the present findings shed light on the pattern of activity levels and drug effects at a frequently studied developmental age [21] For example, the results indicate how potentially important behavioral data can be lost if activity is monitored only at longer time intervals, such as 2 hr blocks A thorough analysis of drug effects on behavior during early development evidently requires attention to both the temporal pattern of behavior, as well as to the detailed topography of specific motor actions The present study may have additional implications regarding the effects of stimulant medications in children with attention deficit hyperactivity disorder ("minimal brain dysfunction"), as our preliminary clinical observations suggest that abnormal ultradian activity patterns may be present in some children with this disorder, and that these abnormalities can be ameliorated by stimulant medications

ACKNOWLEDGEMENTS

Supported in part by USPHS (NIMH) award MH-47370 and grants MH-31154 and MH-36224, grants from the Bruce J Anderson Foundation and Marion Ireland Benton Trust Fund, and an Ethel Dupont Warren Fellowship

REFERENCES

1 Barber, N I , M H Teicher and R J Baldessarini Effects of selective monoaminergic reuptake blockade on ultradian and circadian activity rhythms in developing rats *Eastern Psychol Assoc Abstr* **58:** 29, 1986

2 Beersma, D G , S Daan and R M Van den Hoofdakker Distribution of REM latencies and other sleep phenomena in depression as explained by a single ultradian rhythm disturbance *Sleep* **7:** 126–136, 1984

3 Blackman, R B and J W Tuckey *The Measurement of Power Spectra* New York Dover, 1985

4 Brodsky, W Y Protein synthesis rhythms *J Theor Biol* **55:** 167–200, 1975

5 Busby, K A and R J Broughton Waking ultradian rhythms of performance and motility in hyperkinetic and normal children *J Abnorm Child Psychol* **11:** 431–442, 1983

6 Campbell, B A , L D Lytle and H C Fibiger Ontogeny of adrenergic arousal and cholinergic inhibitory mechanisms in the rat *Science* **166:** 635–637, 1969

7 Corner, M A Sleep and the beginnings of behavior in the animal kingdom—studies of ultradian motility cycles in early life *Prog Neurobiol* **8:** 279–295, 1977

8 del Pozo, F , F V DeFeudis and J M Jiminez Environmentally sensitive ultradian motor rhythms in mice *Naturwissenschaften* **65:** 393–394, 1978

9 del Pozo, F , F V DeFeudis and J M Jiminez Motilities of isolated and aggregated mice A difference in ultradian rhythmicity *Experientia* **34:** 1032–1034, 1978
10 Halberg, F and H Panofsky Thermovariance spectra Method and clinical illustrations *Exp Med Surg* **19:** 284–309, 1961
11 Holaday, J W , H M Martinez and B H Natelson Synchronized ultradian cortisol rhythms in monkeys Persistence during corticotropin infusion *Science* **198:** 56–58, 1977
12 Kellog, C and P Lundborg Ontogenic variations in response to L-DOPA and monoamine receptor-stimulating agents *Psychopharmacologia* **23:** 187–200, 1972
13 Kleitman, N *Sleep and Wakefulness* Chicago University of Chicago Press, 1939
14 Kripke, D F Ultradian rhythms in sleep and wakefulness In *Advances in Sleep Research, Vol 1,* edited by E Weitzman New York Spectrum, 1975, pp 305–325
15 Lange, H EEG spectral analysis in vital depression ultradian cycles *Biol Psychiatry* **17:** 3–21, 1982
16 Lavie, P and D F Kripke Ultradian circa 1 1/2 hour rhythms A multioscillatory system *Life Sci* **29:** 2445–2450, 1981
17 McCarley, R W and J A Hobson Neuronal excitability modulation over the sleep cycle A structural and mathematical model *Science* **189:** 58–60, 1975
18 Millard, W J , S M Reppert, S M Sagar and J B Martin Light-dark entrainment of the growth hormone ultradian rhythm in the rat is mediated by the arcuate nucleus *Endocrinology* **108:** 2394–2396, 1981
19 Okamoto, M , V S Adamon and J L Walenski Effects of d-amphetamine on hypothalamic ultradian temperature and sleep *Pharmacologist* **28:** 190, 1986
20 Panofsky, H and F Halberg Thermovariance spectra Simplified computational example and other methodology *Exp Med Surg* **19:** 323–338, 1961
21 Randall, P K and B A Campbell Ontogeny of behavioral arousal in rats Effect of maternal and sibling presence *J Comp Physiol Psychol* **90:** 453–459, 1976
22 Richter, C P A behavioristic study of the activity of the rat *Comp Psychol Monogr* **1:** 1–55, 1922
23 Richter, C P Animal behavior and internal drives *Q Rev Biol* **2:** 307–343, 1927
24 Rummel, J , J K Lee and F Halberg Combined linear-nonlinear chronobiologic windows by least-squares resolve neighboring components in a physiologic rhythm spectrum In *Biorhythms and Human Reproduction,* edited by M Ferin, F Halberg, R M Richart and R L Vande Wiele New York John Wiley & Sons, 1974, pp 53–82
25 Siegel, S *Nonparametric Statistics for the Behavioral Sciences* New York McGraw-Hill, 1956, pp 47–52
26 Teicher, M H BIRAN I Interactive programs for harmonic spectral analysis of biologic time-series data In preparation
27 Teicher, M H and N I Barber COSIFIT Interactive program for simultaneous non-linear least-squares multioscillator cosinor rhythm analysis of biological time-series data In preparation
28 Teicher, M H , N I Barber, J M Lawrence and R J Baldessarini Motor activity and antidepressant drugs A proposed approach to categorizing depression syndromes and their animal models In *Animal Models of Depression,* edited by D J Kupfer, G Koobs and C Ehler Chicago University of Chicago Press, in press
29 Teicher, M H and L E Flaum The ontogeny of ultradian and nocturnal activity rhythms in isolated albino rats *Dev Psychobiol* **12:** 441–454, 1979
30 Teicher, M H and W T Green A digital readout vibrational activity monitor for neonatal animals *Physiol Behav* **18:** 747–750, 1977
31 Teicher, M H , J M Lawrence, N I Barber, S P Finklestein, H Lieberman and R J Baldessarini Altered locomotor activity in neuropsychiatric patients *Prog Neuro-Psychopharmacol Biol Psychiatry* **10:** 755–761, 1986
32 Wang, D C C and A H Vagnucci TSAN A package for time series analysis *Comput Programs Biomed* **11:** 132–144, 1980