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Automated Measurement of Motor Activity in Human Subjects: Effects of Repeated Testing and *d*-Amphetamine

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GREENWALD, M. K., C. R. SCHUSTER, C.-E. JOHANSON AND J. JEWELL. *Automated measurement of motor activity in human subjects: Effects of repeated testing and* d-*amphetamine.* PHARMACOL BIOCHEM BEHAV **59**(1) 59–65, 1998.—Repeated exposure to a test setting decreases, and amphetamine increases, motor activity in animals. To evaluate whether these effects also occur in human subjects, we recorded motor activity levels from 12 subjects during a double-blind oral drug discrimination (placebo vs. 75 mg tripelennamine) study. Before each 4-h session, activity monitors were attached to the subject's wrist and ankle. During each session, subjects rated their drug effects hourly (task periods), and could freely choose among leisure activities during intertask intervals (recreational periods). Habituation was evaluated by comparing activity response during initial (training phase) vs. later (discrimination phase) placebo sessions. During later sessions the two training drugs, as well as diazepam (2.5, 5 mg PO) and *d*-amphetamine (5, 10 mg PO) were administered. Consistent with animal studies, repeated exposure to the test environment significantly decreased, and *d*-amphetamine significantly and selectively increased, wrist motor activity. These data indicate that human motor activity is sensitive to environmental factors (task, time), drug class, and *d*-amphetamine dose. Activity measures may, therefore, be useful in evaluating environment/psychostimulant interactions in humans. © 1998 Elsevier Science Inc.

Humans Motor activity Exploratory behavior Time factors Habituation Amphetamine Central nervous system stimulants Drug abuse

DIRECT measurement of spontaneous motor activity in animals has played an important role in evaluating the neuropharmacological mechanisms and toxicological consequences of abused drugs (4,28,31,34) and distinguishing topographical features of behavior (5,27,32,35). This extensive literature indicates that motor activity pattern is a complex outcome of both environmental and pharmacological influences. Starting from this central principle, the present research begins to evaluate in human subjects the interactive effects of environment and drugs on spontaneous motor activity.

Motor activity measures are significantly influenced by the animal's history in a test setting. When animals are repeatedly exposed to the same open-field environment, several topographical features of motor (particularly exploratory) behavior are greatest during the first test session, rapidly habituate, and remain relatively stable thereafter (24,27,28,40). A second effect that has been observed numerous times in animals is the ability of psychostimulants such as *d*-amphetamine to produce dose-dependent increases in motor activity [e.g., (8,9, 12,29)]. Low to moderate doses of *d*-amphetamine stimulate locomotion and exploration in animals, whereas high doses can produce stereotypy or suppression of behavior [e.g., (16, 36,37)]. In the low to moderate range of psychostimulant doses that are typically administered to healthy human volunteers, one would expect to observe linear increases in motor activity.

This experiment investigated changes in human motor activity during repeated exposure to a laboratory recreational environment and the effects of various drugs administered in

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this setting. The goals of this study were to 1) assess the reliability and validity of activity measurement in human subjects, including whether (a) activity levels in a laboratory setting exhibit within-session variation due to alternating task performance and free-choice recreational periods, and (b) activity recordings at different anatomical locations (wrist vs. ankle) having potentially different functions (e.g., manual exploration vs. locomotion) are equally sensitive to environmental- and drug-exposure effects; 2) evaluate whether repeated exposure to the testing environment is associated with decreases in activity level (i.e., habituation); and 3) determine whether *d*-amphetamine selectively (relative to placebo and nonstimulant drugs) and dose dependently increases motor activity.

METHOD

Participants

We recruited individuals from the Baltimore community using newspaper advertisements and word of mouth. Volunteers provided a medical history and received a complete physical examination before study participation. The medical screening included an electrocardiogram, blood and urine samples for routine laboratory testing, and broad-spectrum urine toxicology (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and phencyclidine). Psychiatric screening included a semistructured clinical interview, the Addiction Severity Index, and a drug use survey. Those with serious medical problems, psychiatric conditions, current illicit drug use (based on a positive urine or self-report), a history of drug or alcohol dependence other than nicotine dependence, as well as those taking prescription medication, were excluded from participating in the study. The local Institutional Review Board approved this protocol. Each volunteer provided written informed consent.

This study was conducted in the context of a drug discrimination protocol (see below). Because the motor activity study was initiated after the drug discrimination study began, only the 15 final volunteers (out of 30 who entered the discrimination study) were offered the opportunity to participate. Of these 15 subjects, 3 did not complete the activity study (due to actometer malfunction); data from the remaining 12 volunteers form the basis of the present report. Of these 12 subjects, seven were white, four were African American, and one was Hispanic. There were eight male and four female subjects. Mean age was 32.2 years (range = 22–48) and mean educational level was 11.9 years (range = 8–16). Four volunteers reported past marijuana use. One of these four volunteers reported smoking heroin once and cocaine twice. Seven subjects reported current tobacco use; they were permitted to continue their regular smoking habits during study participation, but were restricted from smoking during test sessions. Regular caffeine use by volunteers was not assessed; caffeine use was restricted during test sessions.

Drugs

The antihistamine tripelennamine (75 mg; CibaGeigy Pharmaceuticals, Summit, NJ), diazepam (2.5 and 5 mg; UDL Laboratories, Rockford, IL), *d*-amphetamine (5 and 10 mg; Smith Kline Beecham Pharmaceuticals, Philadelphia, PA), and dextrose placebo were all orally administered in this study using hard gelatin capsules under double-blind conditions.

Procedure

Subjects attended sessions in the outpatient research laboratory on the average of every other day. During the first four sessions (phase 1), the placebo vs. 75 mg tripelennamine discrimination was trained. The four training sessions consisted of two exposures each to placebo and tripelennamine; the first placebo was randomly administered in either session 1 or 2 for each subject. Volunteers' activity response was measured in each session. The activity response during the first placebo training session was defined a priori as the initial response to the environment (novelty). Discrimination training was followed by seven test-of-acquisition sessions [phase 2; three of one drug (placebo or tripelennamine) and four of the other drug, counterbalanced across subjects]. Phase 2 was followed by eight sessions (phase 3) with two placebo exposures, two tripelennamine exposures, and one exposure each to doses of amphetamine (5 and 10 mg) and diazepam (2.5 and 5 mg); order of presentation was counterbalanced across volunteers. It was decided a priori to use the first placebo test exposure during phase 3 as the "repeated" exposure session in analyzing the motor activity data. (Post hoc analyses revealed no significant difference in activity levels between the first and second exposures to placebo in this phase.)

For each session the volunteer came to the laboratory for about 5 h. At the laboratory, the subject provided a urine sample and took a breathalyzer test to verify compliance with the requirements for drug abstinence. Activity monitors (Mini Motionlogger Actigraph, Ambulatory Monitoring, Inc., Ardsley, NY) were then attached firmly to the wrist of the subject's dominant hand and the ankle of the dominant leg using Velcro bands. These wristwatch-size devices contain a piezoelectric transducer that detects motion. Each motor event produces an increase in signal voltage compared with a reference (threshold) voltage, which is translated into one activity "count." The frequency of counts per unit time (default = 20 s) at each recording site were the dependent measures.

Sessions occurred in a recreational environment (furnished room measuring 9.75 m × 5.33 m). After the actigraphs were placed on the volunteer, the study drug was orally administered. Once administered, the subject pressed an event marker button on the activity monitor to denote the start of data collection. The subject also pressed the event marker button at the end of the session. Volunteers were free to engage in different activities provided in the laboratory when tasks were not scheduled; these intertask intervals are thus referred to as "recreational periods," in contrast to "task periods." Activities available during recreational periods were a computer with games, pool table, television, and various reading materials. Volunteers could bring a personal stereo with headphones to use during recreational periods if they did not disturb other volunteers. On the majority of occasions (76% of sessions) a second volunteer was also present in the laboratory, and subjects were free to interact during recreational periods if they wished. Volunteers also had unrestricted bathroom breaks. While in the laboratory, volunteers completed subjective effects forms (e.g., visual analog scale ratings) before drug administration and again at 1, 2, 3, and 4 h after dosing. Subjects had a brief snack scheduled in all sessions at the 2-h time point following questionnaire completion. Volunteers were paid $20 for each session, with a bonus of $10 if their identification of the drug was correct during phase 3 sessions.

Data Reduction and Analysis

Activity monitors are accelerometers that record motor event frequency per unit time. Data were stored in a microprocessor (32 kb memory) built into each monitor. After completing each session, each monitor was docked in the manu-

facturer's Actigraph Interface Unit and data were transferred by serial communication to disk for storage and scoring using manufacturer-supplied software. Based on preliminary graphical analysis, activity data were compressed from the 20-s default intervals into 10-min intervals for each 4 h (postdrug) session. Another reason to select 10-min intervals is that previous animal activity studies have often reported results in 10-min bins. Time points presented in the results reflect the endpoint of the time bin, for example, the 30-min time point is the sum of activity counts from 20–30 min.

Univariate drug condition (six levels: placebo, tripelennamine 75 mg, diazepam 2.5 and 5 mg, and *d*-amphetamine 5 and 10 mg) × session time (24 levels: 10-min postdrug bins) analyses of variance (ANOVAs) were performed on wrist and ankle activity measures. The 10-min bins were ultimately summed into total activity scores (i.e., area under the curve [AUC]) for each session, which represent the drug main effect from ANOVAs. Huynh-Feldt corrected significance levels were used for repeated measures ANOVAs. Tukey honestly significant difference tests were used to make post hoc comparisons between active drug doses and placebo means. Modified Tukey tests (1,17) were used to compare pairs of cell means (e.g., the same session time points during initial vs. repeated exposure to the test setting). Unless otherwise noted, the rejection region for all significance tests was set at $p < 0.05$ (two-tailed α).

RESULTS

Effects of Repeated Exposure to Test Environment

Throughout the study, mean wrist activity levels were greater than mean ankle activity levels; this pattern was consistent across individuals and drug conditions. Directional effects (increases and decreases across time and by drug condition) were similar, but less pronounced for ankle than wrist activity. This led to greater sensitivity for the wrist than the ankle site in statistical analyses. Figure 1 illustrates average wrist activity (left panel) and ankle activity (right panel) during each subject's initial placebo exposure session, compared with activity levels during a later placebo session (i.e., intermixed with all drug conditions). Activity levels exhibited cyclical variation that was associated with events in the laboratory, wrist: time $F(23, 253) = 2.19$, $p < 0.05$; ankle: time $F(23, 253) = 2.00$, $p < 0.05$. At the 1-h, 2-h, and 3-h session time points, activity levels increased when volunteers provided pencil-and-paper reports of their subjective drug effects; these activity increases subsided after task completion. Overall, the time–activity curves in each panel of Fig. 1 show similar patterns during most of the session. Nevertheless, activity response differed significantly after repeated exposure to the laboratory setting compared to the initial placebo session. Wrist activity levels were significantly lower at most time

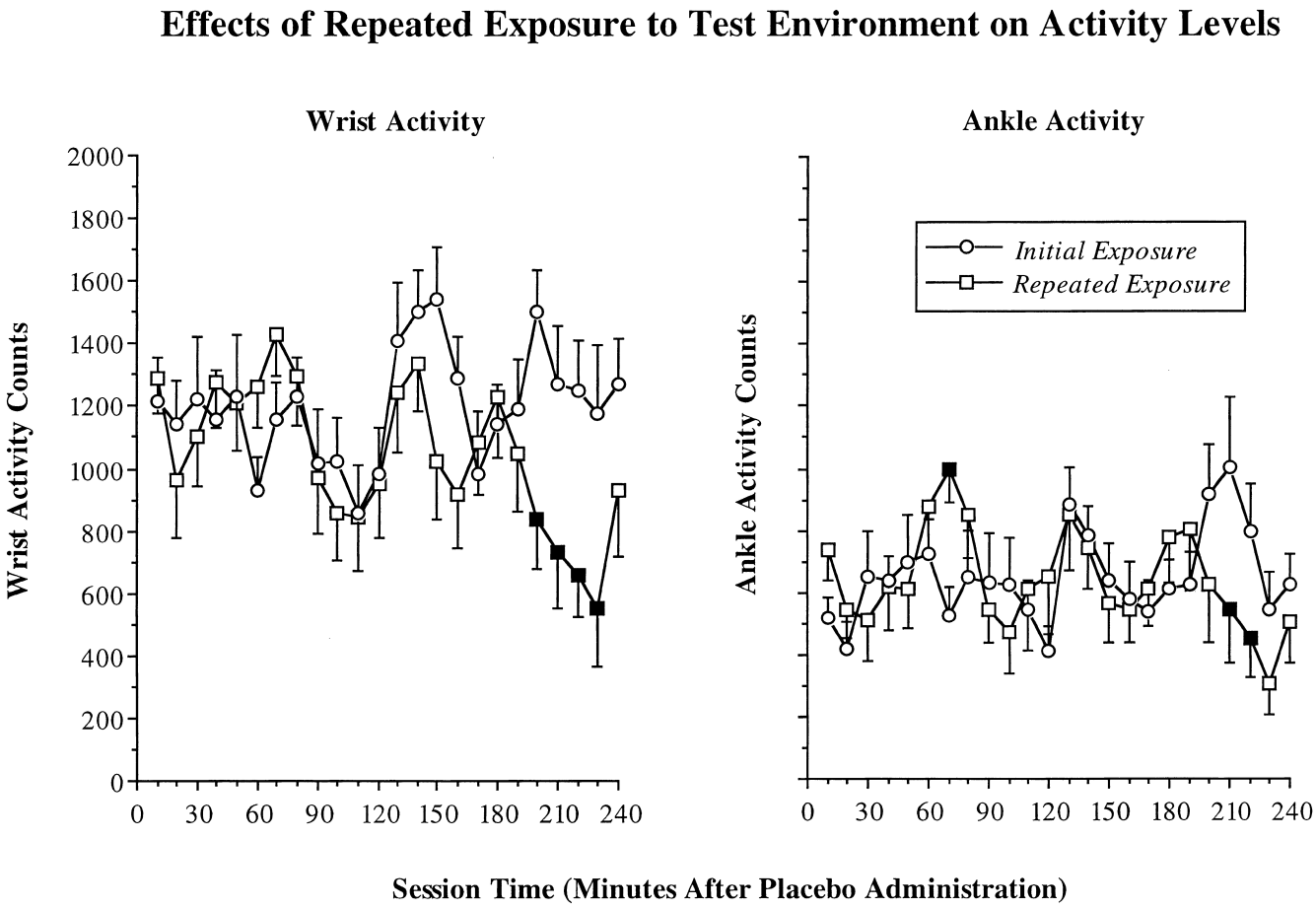

FIG. 1. Mean (per 10 min, + SEM) wrist activity (left panel) and ankle activity (right panel) levels during initial exposure to the recreational environment (circles) vs. after repeated exposure to the same test setting (squares) under placebo conditions. Dark icons indicate a significant repeated exposure effect at the respective session time points, as determined by Tukey post hoc testing.

points during the final hour of the later session in the series than at comparable time points in the initial placebo session, occasion × time $F(23, 253) = 1.93$, $p < 0.02$; this was confirmed by post hoc tests (dark icons in Fig. 1; mean wrist activity per 10 min during the last hour for initial and repeated placebo sessions was 1276 and 796 units, respectively). A similar, significant pattern was found for ankle activity, occasion × time $F(23, 253) = 1.83$, $p < 0.05$. These data are consistent with the hypothesis that repeated environmental exposure (under placebo conditions) engenders habituation, which is more evident when the subject remains in the setting for a sufficiently long interval.

Response to d-*Amphetamine and Control Drugs*

As predicted, *d*-amphetamine selectively increased spontaneous motor activity relative to other drug conditions. This effect depended on recording site, dose, and session time. Figure 2 shows motor activity during the 4-h session in four of the six drug conditions (excluding the low doses of *d*-amphetamine and diazepam). Mean differences in wrist activity among conditions fluctuated across the session, drug × time $F(115, 1265) = 1.38$, $p < 0.06$. The 10 mg dose of *d*-amphetamine maintained generally high activity levels during the 4-h test session, whereas wrist activity in all other drug conditions showed cyclic increases and decreases. Times of generally increased activity (regardless of drug condition) were associated with the hourly demand for volunteers to answer subjective effects questionnaires (i.e., task periods). Post hoc tests indicated that, at several time points (dark icons in Fig. 2), motor activity response to 10 mg *d*-amphetamine significantly exceeded one or more nonstimulant conditions, i.e., either placebo, tripelennamine, or 5 mg diazepam, but not 5 mg *d*-amphetamine. Relative to placebo, neither tripelennamine nor diazepam produced significant decreases in activity.

The failure to see increases in activity during hourly questionnaire interludes in the 10 mg *d*-amphetamine condition might suggest a ceiling effect. Individual subject data for this condition revealed that, for about half of the subjects, peak activity tended to occur during questionnaire completion. However, the other subjects did not clearly demonstrate this effect. Therefore, it does not appear that the continuous elevations in activity for this condition are due to a ceiling effect. Differences in ankle activity between drug conditions were not significant, drug $F(5, 55) = 0.66$, $p = 0.58$; drug × time $F(115, 1265) = 1.18$, $p = 0.27$. Figure 2 clearly shows that the magnitude of *d*-amphetamine's activity-increasing effect was enhanced during recreational periods compared with task periods (i.e., the four data points at times 70, 130, 140, and 190 min, shown in the shaded vertical bars, which reflect subjective effects forms completion and snack time).

Figure 3 presents mean wrist and ankle scores for all conditions. Mean drug dose effects were calculated across the entire 4-h time course, as well as during recreational periods only to obtain a more accurate measure of spontaneous motor activity. The overall stimulation effect from *d*-amphetamine was significant at the wrist site when including all session time points, drug $F(5, 55) = 3.30$, $p < 0.02$, and when data for only recreational periods were used in the analysis, $F(5, 55) = 3.45$, $p < 0.02$. Post hoc tests confirmed that 10 mg *d*-amphetamine produced activity changes that were significantly different from all conditions except 5 mg *d*-amphetamine. The 5 mg dose showed a smaller increase but did not significantly differ from other conditions. Figure 3 also illustrates that *d*-amphetamine's activity-increasing effects were proportional to dose.

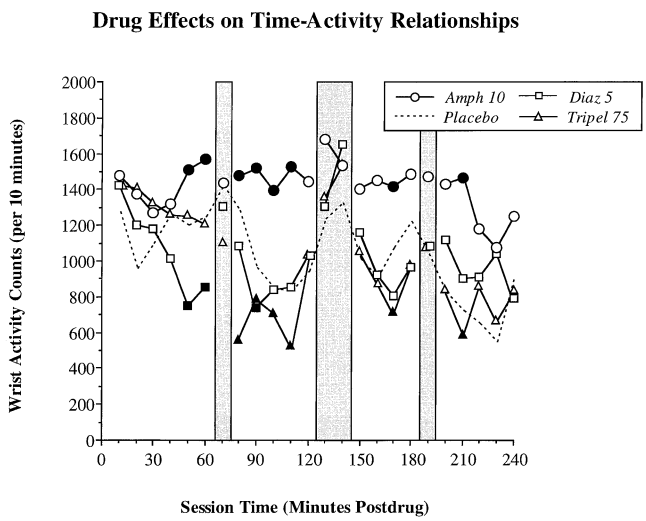

FIG. 2. Session time course of wrist activity changes after four of the six oral drug administrations: 10 mg *d*-amphetamine, 5 mg diazepam, 75 mg tripelennamine, and placebo. Dark icons at each time point indicate that mean response to 10 mg *d*-amphetamine and at least one other drug condition significantly differed, based on Tukey tests (critical difference score = 689 activity units).

Specifically, 5 and 10 mg doses produced wrist activity increases of 17 and 37% above placebo response including all session points, and 20 and 41% above placebo during recreational periods. These doses produced fractionally smaller ankle activity increases of 11 and 22% above placebo response including all session points, and 17 and 19% above placebo during recreational periods. Finally, relative to the initial placebo session mean response (dashed lines in Fig. 3), *d*-amphetamine increased activity, whereas the remaining conditions were associated with decreased activity. Thus, only *d*-amphetamine abated the general trend for between-session habituation.

Measures of ankle and wrist activity were qualitatively similar in this study. The magnitude of the correlations between wrist and ankle activity AUC scores within each drug condition provide evidence of convergent validity. Wrist and ankle activity significantly covaried for active drug conditions (r values = 0.49 to 0.78, p values < 0.05), whereas the wrist–ankle activity correlation for placebo was 0.29 (NS). Further, there were strong positive correlations between activity levels across two doses of the same drug: ankle activity scores for 2.5 and 5 mg diazepam were highly correlated ($r = 0.92$), and ankle activity for 5 and 10 mg *d*-amphetamine were highly correlated ($r = 0.94$). Wrist activity scores for 2.5 and 5 mg diazepam were also highly correlated ($r = 0.93$), whereas the relation between wrist activity for 5 and 10 mg *d*-amphetamine was positive but not significant ($r = 0.38$).

DISCUSSION

To our knowledge, the present study is the first to describe the spontaneous motor activity of human volunteers in a recreational environment, to compare the dose- and time-related effects of *d*-amphetamine (relative to nonstimulant drugs and placebo) upon activity in this outpatient laboratory setting, and to examine the influence of repeated exposure to the laboratory environment on motor activity levels. These data were collected to establish a basis for future human behav-

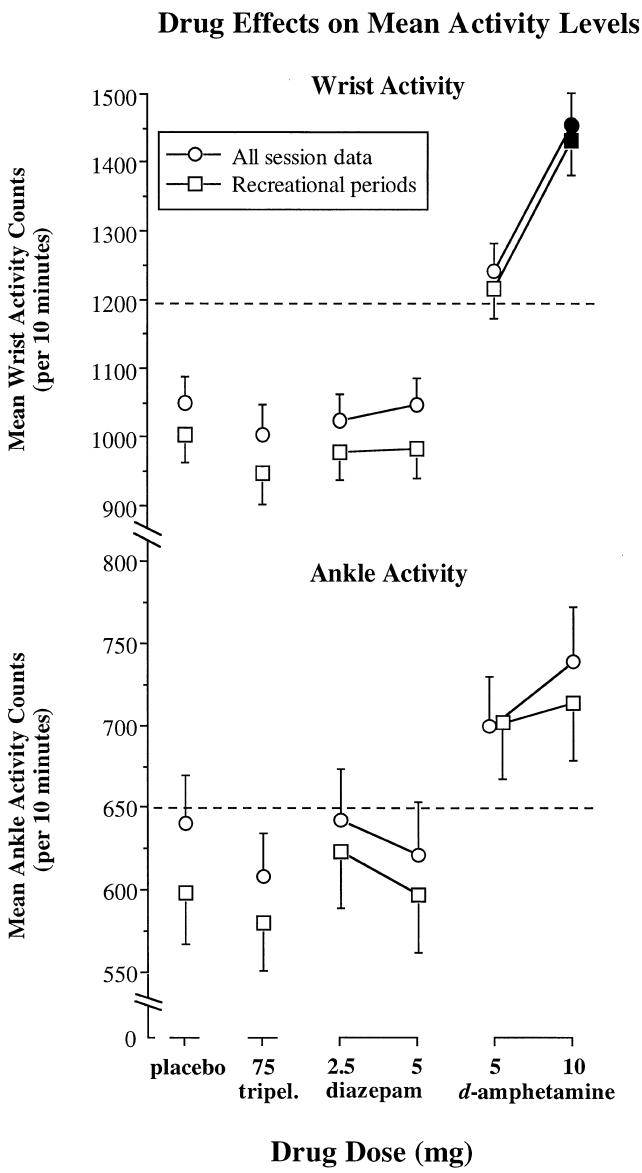

FIG. 3. Drug dose–effect curves for mean (per 10 min, + SEM) wrist and ankle response in each drug condition. Circles indicate data for all time points, whereas squares indicate data for only the recreational periods (see Fig. 2). Only 10 mg *d*-amphetamine produced a significant mean increase above placebo at the wrist recording site (darkened icons). Dashes in each panel indicate the mean (wrist or ankle) score in the initial placebo exposure session (see Fig. 1).

ioral pharmacological testing and to evaluate whether motor activity patterns in human subjects mimic previous findings in animals. Animal studies of activity level have usually measured locomotion and/or exploratory behavior. Accordingly, we placed activity monitors at two anatomical sites (i.e., ankle and wrist) that might reflect topographically similar behaviors in humans. Subjects exhibited significantly greater wrist activity than ankle activity overall, and wrist activity was more sensitive to environment- and drug-related effects. Nevertheless, ankle activity changes were both directionally and proportionally similar to those observed at the wrist recording site.

Effects of Repeated Exposure to Test Environment

Activity levels in the recreational setting under placebo conditions systematically varied within sessions (i.e., change as a function of session time) and between sessions [i.e., change between initial exposure (novelty) and repeated exposure to the setting]. During the 4-h session, activity levels at both wrist and ankle sites exhibited cyclical variation that was associated with task-related events. Specifically, the experimental demand for volunteers to answer subjective drug effects questionnaires beginning each hour after drug administration and lasting about 10 min was related to phasic increases in motor activity level, whereas activity during recreational periods was relatively lower. Individual subjects' data consistently showed this cyclical effect. The entrainment of motor activity to environmental demands supports the hypothesis that the quantitative activity measures used here are reliable and valid. Although periodic changes in activity observed in this study could correspond to basic rest–activity cycles averaging about 90 min in length (18) this is unlikely because the only studies that have reliably found such periodicity involve isolating the subject and not imposing environmental demands (7,19,26).

Activity levels during volunteers' initial placebo sessions in the recreational setting were greater than after repeated (placebo) exposure to the same setting, mostly the result of declining levels near the end of the repeated exposure session (Fig. 1). This finding is consistent with animal studies (24,27,28,40) in showing that spontaneous motor activity habituates with repeated exposure. Because this study was opportunistic (i.e., the sequence of drug exposures was determined by the constraints of the discrimination study), the present findings must be cautiously interpreted. Furthermore, what constitutes "novelty" in the setting of typical animal studies (e.g., an open-field test for rodents) is probably quite different than the experience of human subjects exposed (initially and repeatedly) to a stimulus-rich recreational environment such as that in this study. The lack of an analogous "novelty" situation in human and infrahuman species makes comparison of habituation data challenging. One may conjecture that our human volunteers had probably (if not regularly) encountered similar leisure settings before and, through their learned associations in this situation, did not find it wholly "novel." This could potentially explain the relatively modest (albeit statistically significant) habituation of activity levels observed upon repeated testing.

Although decreased activity response during the repeated placebo session might be attributed to decreased exploratory activity (i.e., particularly the wrist site), this study was not designed to distinguish exploratory activity from other types of activity (e.g., stereotypy, locomotion). Future studies in which the environment is manipulated to require subjects to make exclusive choices between exploratory vs. nonexploratory activities (33), and the concomitant use of videotape monitoring to capture molar behavior, could provide information on qualitative differences in activity patterns. Nevertheless, direct automated measurement of activity is easily accomplished, possesses unique quantitative sensitivity and, therefore, would seem ideal to retain as a central component of future evaluations.

Response to d-*Amphetamine and Control Drugs*

d-Amphetamine increased overall motor activity level relative to placebo. The 5-mg dose produced a modest, nonsignificant increase from placebo levels whereas 10 mg produced a proportionally larger, significant effect. These data are consistent with previous animal studies showing that systemically administered, low-to-moderate doses of *d*-amphetamine (0.025

to 0.4 mg/kg), i.e., within the therapeutic range, increase activity (8,9,29). In these animal studies, total movement after a 0.09 mg/kg (29) and a 0.1 mg/kg dose (9) increased by about 50% above placebo response. In the present study, a comparable dose of 10 mg (approximately 0.14 mg/kg) produced a 40% wrist activity increase and a 20% ankle activity increase, relative to placebo. Thus, ankle activity changes were directionally similar to but less robust than wrist activity changes, whereas the extent of wrist activity increase was comparable with effects in previous animal studies.

The experimental procedures used in this study, i.e., periodic task performance alternating with recreational periods, help to qualify interpretation of the activity measures. An interesting feature of the response to 10 mg *d*-amphetamine was that absolute wrist activity remained consistently higher throughout the session, whereas response in the other conditions was greater during task periods and decreased during recreational periods. Thus, there was maximal differentiation between *d*-amphetamine and other drug conditions during recreational periods (Fig. 2). The peak *d*-amphetamine 10 mg vs. placebo difference during the recreational periods was about 55%, which is equivalent to activity increases produced by similar doses in previous animal studies. The present data are consistent with the hypothesis that modest doses of *d*-amphetamine may suppress habituation to the environment when there are no external demands on the subject; however, a direct test of this hypothesis remains to be conducted. The data further suggest that if the research objective is to optimize differences among drug conditions, then it may be preferable to measure spontaneous motor activity in a free-choice recreational context, i.e., without scheduled task periods.

d-Amphetamine-induced motor activity increases in this study are consistent with increased subjective reports of stimulation/energy from this drug in previous human studies [e.g., (3,14,38)]. Volunteers in the present study could have been similarly aroused after 10 mg *d*-amphetamine, leading to the relatively greater activity response compared with other conditions (especially during the recreational periods). Previous human studies have also shown that doses of diazepam 5 mg and greater (15,17,21,22) and tripelennamine doses of 50 mg and greater (13,39) can render subjects significantly more sedated and less stimulated. These results suggest that the modest doses of diazepam and tripelennamine selected for this study might have decreased motor activity. Although these drug doses did not significantly decrease overall wrist or ankle activity levels relative to placebo, they did produce significantly less activity at some time points during the 4-h session and overall relative to 10 mg *d*-amphetamine (see Figs. 2 and 3). Although the effects of diazepam and tripelennamine on spontaneous motor activity have not been previously studied in human subjects, diazepam's effects on psychomotor performance have been examined. Unlike moderate to high doses of diazepam (i.e., $\geqslant$10 mg/70 kg), acute low doses do not reliably impair psychomotor performance in healthy young volunteers (6,20). It may be that relatively low doses of diazepam and tripelennamine do not produce large psychomotor effects, although this may depend on the psychomotor measures used and, as noted above, the sample size and environmental setting. In future research, it would be useful to examine spontaneous motor activity effects with higher doses of these sedating drugs, as well as the activity-altering effects of other alerting substances such as over-the-counter medications (e.g., caffeine, decongestants).

Finally, the mean activity response to *d*-amphetamine exposure was greater than mean response to initial placebo which, in turn, was greater than mean response to placebo and the nonstimulant drugs diazepam and tripelennamine (Fig. 3). This pattern of results suggests that it may be more difficult to detect a significant effect of *d*-amphetamine (or other psychostimulant drugs) under conditions of environmental novelty. This "signal-to-noise" (i.e., drug vs. environment effect) problem could be especially vexing when trying to detect activity increases from relatively lower drug doses, as in the present study. The present findings imply that the ability to detect significant drug effects depends not only on drug dose and sample size, but also on subjects' familiarization with the test setting (23), test session length, and whether tasks are to be performed during the session.

In summary, this study establishes the validity of automated procedures to measure human motor activity in a controlled laboratory context. Motor activity exhibited periodic changes that corresponded to scheduled task performance (i.e., relative increases in activity) vs. free-choice recreational activity (i.e., relative decreases). Motor activity under placebo conditions decreased (habituated) with repeated exposure to the laboratory setting. Consistent with animal studies, *d*-amphetamine produced significant increases in activity that were greater for 10 mg than 5 mg. In contrast, at the doses tested in this study, motor activity was not significantly altered by the administration of diazepam and tripelennamine. Actometric recordings from the wrist site were generally more sensitive to both environment- and drug-related effects than activity at the ankle site, demonstrating anatomical (and, perhaps, functional) specificity. These observations provide methodological groundwork to begin formal investigation of the role of human motor activity in relationship to drug abuse [e.g., (41)]. For example, animal studies have shown a positive relationship between activity response to environmental novelty and psychostimulants, and that these measures are related to acquisition of drug self-administration (2,10,11,30), suggesting that it would be worthwhile to explore in humans whether individual differences in motor activity might be related to substance abuse vulnerability [e.g., (25)].

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REFERENCES

1. Cichetti, D. V.: Extension of multiple-range tests to interaction tables in the analysis of variance: A rapid approximate solution. Psychol. Bull. 77:405–408; 1972.
2. Deminiere, J. M.; Piazza, P. V.; Le Moal, M.; Simon, H.: Experimental approach to individual vulnerability to psychostimulant addiction. Neurosci. Biobehav. Rev. 13:141–147; 1989.
3. de Wit H.; Uhlenhuth, E. H.; Johanson, C. E.: Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. Drug Alcohol Depend. 16:341–460; 1986.
4. Geyer, M. A.: Approaches to the characterization of drug effects on locomotor activity in rodents. In: Modern methods of pharmacology, vol. 6, Testing and evaluation of drugs of abuse. New York: Wiley-Liss; 1990:81–99.
5. Geyer, M. A.; Paulus, M. P.: Multivariate and nonlinear approaches

to characterizing drug effects on the locomotor and investigatory behavior of rats. In: Frascella, J.; Brown, R. M., eds. Neurobiological approaches to brain–behavior interaction, NIDA research monograph 124. Washington, DC: U.S. Government Printing Office; 1992:203–233.
6. Ghoneim, M. M.; Mewaldt, S. P.; Hinrichs, J. V.: Dose–response analysis of the behavioral effects of diazepam: II. Psychomotor performance, cognition and mood. Psychopharmacology (Berlin) 82:296–300; 1984.
7. Grau, C.; Escera, C.; Cilveti, R.; Garcia, M.; Mojon, A.; Fernandez, J. R.; Hermida, R.: Ultradian rhythms in gross motor activity of adult humans. Physiol. Behav. 57:411–419; 1995.
8. Hienz, R. D.; Turkkan, J. S.; Spear, D. J.; Sannerud, C. A.; Kaminski, B. J.; Allen, R. P.: General activity in baboons measured with a computerized, lightweight piezoelectric motion sensor: Effects of drugs. Pharmacol. Biochem. Behav. 42:497–507; 1992.
9. Holtzman, S. G.; Young, C. W.: Motor activity of squirrel monkeys measured with an ultrasonic motion sensor. Pharmacol. Biochem. Behav. 38:633–637; 1991.
10. Hooks, M. S.; Jones, G. H.; Smith, A. D.; Neill, D. B.; Justice, J. B., Jr.: Individual differences in locomotor activity and sensitization. Pharmacol. Biochem. Behav. 38:467–470; 1991.
11. Hooks, M. S.; Jones, G. H.; Smith, A. D.; Neill, D. B.; Justice, J. B., Jr.: Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse 9:121–128; 1991.
12. Jackson, D. M.; Johansson. C.; Lindgren, L. M.; Bengtsson, A.: Dopamine receptor antagonists block amphetamine and phencyclidine-induced motor stimulation in rats. Pharmacol. Biochem. Behav. 48:465–471; 1994.
13. Johanson, C. E.; Evans, S.; Henningfield, J.: The discriminative stimulus effects of tripelennamine in humans. Psychopharmacology (Berlin) 126:140–146; 1996.
14. Johanson, C. E.; Uhlenhuth, E. H.: Drug preference and mood in humans: *d*-Amphetamine. Psychopharmacology (Berlin) 71:275–280; 1980.
15. Johanson, C. E.; Uhlenhuth, E. H.: Drug preference and mood in humans: Diazepam. Psychopharmacology (Berlin) 71:269–273; 1980.
16. Kelly, P. H.; Seviour, P. W.; Iversen, S. D.: Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. 94: 507–522; 1975.
17. Keppel, G.: Design and analysis: A researcher's handbook, 2nd ed. Englewood Cliffs, NJ: Prentice Hall Inc.; 1982.
18. Kleitman, N.: Basic rest-activity cycle—22 years later. Sleep 5:311–317; 1982.
19. Kripke, D. F.; Wyborney, V. G.; Mullaney, D. J.; Messin, S.; Atkinson, M.: No basic rest-activity cycle in the wrist. Sleep Res. 6:218; 1977.
20. Linnoila, M.; Erwin, C. W.; Brendle, A.; Simpson, D.: Psychomotor effects of diazepam in anxious patients and healthy volunteers. J. Clin. Psychopharmacol. 3:88–96; 1983.
21. Loke, W. H.; Hinrichs, J. V.; Ghoneim, M. M.: Caffeine and diazepam: Separate and combined effects on mood, memory and psychomotor performance. Psychopharmacology (Berlin) 87:344–350; 1985.
22. Mattila, M.; Seppala, T.; Mattila, M. J.: Combined effects of buspirone and diazepam on objective and subjective tests of performance in healthy volunteers. Clin. Pharmacol. Ther. 40:620–626; 1986.
23. Mazurski, E. J.; Beninger, R. J.: Stimulant effects of apomorphine and (+)-amphetamine in rats with varied habituation to test environment. Pharmacol. Biochem. Behav. 29:249–255; 1988.
24. Mead, L. A.; Hargreaves, E.L.; Ossenkopp, K. P.; Kavaliers, M. A multivariate assessment of spontaneous locomotor activity in the Mongolian gerbil (Meriones unguiculatus): Influences of age and sex. Physiol. Behav. 57:893–899; 1995.
25. Moss, H. B.; Blackson, T. C.; Martin, C. S.; Tarter, R. E.: Heightened motor activity level in male offspring of substance abusing fathers. Biol. Psychiatry 32:1135–1147; 1992.
26. Okudaira, N.; Kripke, D. F.; Webster, J. B.: No basic rest-activity cycle in the head, wrist or ankle. Physiol. Behav. 32:843–845; 1984.
27. Ossenkopp, K. P.; Macrae, L. K.; Teskey, G. C.: Automated multivariate measurement of spontaneous motor activity in mice: Time course and reliabilities of the behavioral measures. Pharmacol. Biochem. Behav. 27:565–568; 1987.
28. Ossenkopp, K. P.; Mazmanian, D. S.: The measurement and integration of behavioral variables: Aggregation and complexity as important issues. Neurobehav. Toxicol. Teratol. 7:95–100; 1985.
29. Ott, D. A.; Mandel, R. J.: Amphetamine sensitivity in open-field activity vs. the prepulse inhibition paradigm. Brain Res. Bull. 37: 219–222; 1995.
30. Piazza, P. V.; Deminiere, J. M.; Le Moal, M.; Simon, H.: Factors that predict individual vulnerability to amphetamine self-administration. Science 245:1511–1513; 1989.
31. Reiter, L. W.; MacPhail, R. C.: Motor activity: A survey of methods with potential use in toxicity testing. In: Geller, I.; Stebbins, W. C.; Wayner, M. J., eds. Test methods for definition of effects of toxic substances on behavior and neuromotor function, vol. 1 (Suppl. 1). New York: Ankho International Inc.; 1979:53–66.
32. Robbins, T. W.: A critique of the methods available for the measurement of spontaneous motor activity. In: Iversen, L. L.; Iversen, S. D., eds. Handbook of psychopharmacology, vol. 7. New York: Plenum Press; 1977:37–82.
33. Robbins, T. W.; Iversen, S. D.: A dissociation of the effects of *d*-amphetamine on locomotor activity and exploration in rats. Psychopharmacologia 28:155–164; 1973.
34. Sanberg, P. R.; Hagenmeyer, S. H.; Henault, M. A.: Automated measurement of multivariate locomotor behavior in rodents. Neurobehav. Toxicol. Teratol. 7:87–94; 1985.
35. Sanberg, P. R.; Zoloty, S. A.; Willis, R.; Ticarich, C. D.; Rhoads, K.; Nagy, R. P.; Mitchell, S. G.; Laforest, A. R.; Jenks, J. A.; Harkabus, L. J.; Gurson, D. B.; Finnefrock, J. A.; Bednarik, E. J.: Digiscan activity: Automated measurement of thigmotactic and stereotactic behavior in rats. Pharmacol. Biochem. Behav. 27:569–572; 1987.
36. Schiorring, E.: An open field study of stereotyped locomotor activity in amphetamine treated rats. Psychopharmacology (Berlin) 66:281–287; 1979.
37. Smith, C. B.: Effects of *d*-amphetamine upon operant behavior of pigeons: Enhancement by reserpine. J. Pharmacol. Exp. Ther. 146: 167–174; 1964.
38. Smith, R. C.; Davis, J. M.: Comparative effects of *d*-amphetamine, l-amphetamine and methylphenidate on mood in man. Psychopharmacology (Berlin) 53:1–12; 1977.
39. Stern, K. N.; Chait, L. D.; Johanson, C. E.: Reinforcing and subjective effects of oral tripelennamine in normal human volunteers. Behav. Pharmacol. 1:161–167; 1989.
40. Ukai, M.; Kobayashi, T.; Kameyama, T.: Effects of several amnesic drugs on the habituation of exploratory activity in mice as indexed by horizontal and vertical activities. Gen. Pharmacol. 25:179–85; 1994.
41. Wise, R. A.; Bozarth, M. A.: A psychomotor stimulant theory of addiction. Psychol. Rev. 94:469–492, 1987.