Parallels between Attention Deficit Hyperactivity Disorder and Behavioral Deficits Produced by Neurotoxic Exposure in Monkeys

Deborah C. Rice

U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, D.C., USA

Attention deficit hyperactivity disorder (ADHD) is a disability that affects between 3 and 7% of children, with a significant number of individuals continuing to be affected into adolescence and adulthood. ADHD is characterized in part by an inability to organize complex sequences of behavior, to persist in the face of distracting stimuli, and to respond appropriately to the consequences of past behavior. There are some parallels between the features of ADHD and the behavior of monkeys exposed developmentally to lead or polychlorinated biphenyls (PCBs), as evidenced by research from our laboratory. Both lead and PCB exposure produce deficits on discrimination reversal and spatial delayed alternation performance; treated monkeys exhibit deficits in their ability to change an already established response strategy and inhibit inappropriate responses. Monkeys exposed developmentally to lead or PCBs also perform differently from control monkeys on a fixed interval schedule of reinforcement, which requires the temporal organization of behavior using only internal cues. Whereas the etiology of ADHD is multifactorial, the possibility that neurotoxic agents in the environment contribute to the incidence of ADHD warrants attention. *Key words*: ADHD, attention deficit hyperactivity disorder, behavioral impairment, delayed alternation, discrimination reversal task, fixed interval schedule, lead, monkey model, PCBs. — *Environ Health Perspect* 108(suppl 3):405–408 (2000).
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Attention deficit hyperactivity disorder (ADHD) is a potentially devastating disability that is estimated to affect between 3 and 7% of children (*1–3*). ADHD affects behavior in numerous domains, with the result that "individuals with ADHD cannot depend upon themselves to control their own behavior" (*2*). A significant proportion of children with ADHD will continue to be affected as adolescents, and as many of 50% of these will continue to be affected as adults, making ADHD a lifelong disability.

Individuals with ADHD exhibit impairment in behavioral processes that are typically described as executive functions. One salient feature of ADHD is an inability to organize behavior in time: that is, to plan and execute tasks in an efficient or sensible temporal sequence. Individuals with ADHD exhibit an inability to persist in the face of distracting or competing stimuli. They also show deficient ability to appropriately respond to the consequences of past behavior, even though ADHD is not characterized by reduced intelligence. ADHD is characterized by a deficit in the ability to hold information "online" so that it may be used to consider past events when planning present or future behavior. Thus, persons with ADHD behave impulsively and appear unable to pay attention to the task at hand.

It has been hypothesized that neuroanatomical abnormality of the prefrontal cortex underlies the deficits observed in ADHD (*4–6*), although other brain areas, particularly certain areas intimately connected to the prefrontal cortex, may also be involved (*7–9*). Specific areas of prefrontal cortex are involved in the executive functions: in particular, temporal organization of behavior, ability to respond appropriately to the consequences of previous actions, and the ability to stay on task in the presence of competing stimuli. Whereas it is difficult to identify exact parallels between human behavior and performance by monkeys on tasks assessed in the laboratory, there are nonetheless commonalities in the underlying behavioral processes subserving behavior in both humans and monkeys. It has been suggested that many of the behavioral deficits produced by the neurotoxicants lead and polychlorinated biphenyls (PCBs) are consistent with damage to prefrontal cortex (*10,11*), based largely on an extensive literature on the effects of lesions on many brain areas of monkeys, as well as more recent findings using electrophysiological and functional brain imaging techniques. I present selected examples of research from my laboratory on the effects of developmental exposure to lead or PCBs. The deficits observed share similarities with aspects of behavioral deficits of ADHD.

Behavioral Effects of Developmental Lead or PCB Exposure—Similarities with ADHD

Developmental exposure to lead results in impairment in a number of behavioral domains in animals, including monkeys and rodents (*12*). Developmental PCB exposure also produces a variety of behavioral deficits in rodents and monkeys (*13,14*). Two hallmarks of ADHD will be discussed with respect to the effects of developmental exposure to lead or PCBs using data in monkeys from my laboratory: the inability to learn from the consequences of previous behavior and the inability to organize the temporal sequencing of behavior.

The nonspatial discrimination task proved sensitive to impairment by both lead and PCBs in a number of laboratories. In this task, the subject is required to choose a particular stimulus (e.g., a cross instead of a square) irrespective of which of two positions at which it appears on any given opportunity to choose (defined as a trial). When the performance reaches a specified level of accuracy (e.g., 90% correct across a set of trials), the correct stimulus becomes the incorrect one and vice versa (i.e., a discrimination reversal is implemented). An experiment typically includes a series of such reversals using the same pair of stimuli to ascertain the subject's ability to change response strategy increasingly more quickly on succeeding reversals.

That lead produces impaired performance on this task has been demonstrated in a number of studies. As one example, in our laboratory we assessed performance on this task in a cohort of monkeys in which one group was exposed to lead beginning at birth and continuing throughout the course of study, another group was exposed during infancy only, and a third group was exposed beginning after infancy and continuing throughout the remainder of the study. Steady-state blood lead concentrations during dosing were approximately 20 μg/dL. When tested as juveniles at about 3 years of age, all lead-treated groups were impaired over the course of 15 reversals relative to controls (Figure 1) (*15*). Of particular interest is the fact that

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Address correspondence to D. Rice, EPA/NCEA, MC 8623 D, Washington, DC 20460 USA. Telephone: (202) 564-3404. Fax: (202) 565-0061. E-mail: rice.deborah@epa.gov

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The groups that received the most lead were most impaired on the first reversal (the first time they were required to change a previously learned response).

A similar effect was observed on the identical task in a group of monkeys dosed from birth to 20 weeks of age with a mixture of PCB congeners representative of the congener pattern found in human breast milk (*16*). At 20 weeks, monkeys of this species are still infants. Peak blood PCB concentrations at the end of dosing were approximately 1.5–3.0 ppb, well within the range observed in human populations. When tested as juveniles, some individuals made many more errors over the first several reversals than did control monkeys (Figure 2). This pattern represents a deficit in the ability to adapt to a required change in the response to a set of external stimuli. In fact, it represents a failure to recognize that response requirements may change from time to time in a systematic manner. The inability to predict such patterns and respond appropriately is a hallmark of ADHD.

Interestingly, children with ADHD (*17–19*), as well as children exposed to lead (*20*), exhibit impaired performance on the Wisconsin Card Sort Test. This task is similar to the discrimination reversal task in that it requires the subject to reverse an already established response strategy (e.g., switch from attending to the number on the card to attending to the suit). The subject must determine that a new strategy is required on the basis of the result of response choices, without explicit instruction. Monkeys exposed to lead in our laboratory also displayed deficits when required to change the relevant stimulus dimension (e.g., to switch from "ignore the color and attend to the form" on a series of reversals to "ignore the form and attend to the color" on a subsequent series of reversals).

Spatial delayed alternation also proved sensitive to impairment as a result of developmental lead or PCB exposure. This task requires the subject to simply alternate responses between two positions from trial to trial. There are no external cues that indicate which position is correct, thereby necessitating the use of internal cues to choose the correct position. Delays between opportunities to respond, from a few seconds to a minute or more, may be interposed to make additional demands on the subject. As is true for discrimination reversal performance, the ability of lead to disrupt delayed alternation performance has been repeatedly demonstrated (*21,22*). In another study in our laboratory, a group of monkeys was exposed to lead continuously beginning at birth, resulting in steady-state blood lead concentrations of approximately 10 µg/dL. The monkeys exhibited a dose-related increase in the number of errors on this task, with performance becoming relatively more impaired compared to control monkeys as the delay interval was increased from 0 to 15 sec (*21*). The increase in error rate was largely the result of repeatedly responding on the wrong position, trial after trial, without switching to the correct position (Figure 3). This perseverative responding in some cases continued for dozens of responses in a row, a deficit comparable to some types of brain lesions.

Impaired performance on spatial alternation tasks has also been observed as a consequence of developmental exposure to PCBs in several studies. Performance on this task was assessed in our laboratory in the cohort of monkeys discussed previously, in which the monkeys were exposed to an environmentally relevant congener mixture from birth to 20 weeks of age. As was the case with lead, PCB-treated monkeys exhibited deficits on this task when tested as adults (*16*). Treated monkeys displayed retarded acquisition of the task, manifested as an increase in the number of sessions required to meet the criterion for accurate performance (90% correct) (Figure 4). PCB-exposed monkeys demonstrated increased impairment during the first phase of the experiment as the delay value was increased across blocks of sessions from 0 to 30 sec. During the second phase of the experiment, in which delays of 1–60 sec were tested during the same session, the PCB-treated group was unimpaired as measured by the total number of errors (Figure 5). However, like monkeys exposed to lead, PCB-exposed monkeys exhibited an increase in perseverative errors: i.e., repeatedly choosing the incorrect position after an initial error. Whereas perseverative behavior has not been considered a hallmark of ADHD, such behavior does represent an inability to respond appropriately to the consequences of previous choices (learn from past mistakes), which is a characteristic of ADHD. It is tempting to speculate that perseveration may represent an aspect of impulsivity, which is also associated with ADHD. In the present example, monkeys continued to respond using their preferred hand, and were apparently unable to inhibit that impulse in the face of negative consequences (in this case, no reward and a repeat of the requirement to switch hands).

The final example to be presented is a task that assessed the monkeys' abilities to organize the temporal sequence of behavior; deficits in the temporal organization of behavior are a salient feature of ADHD (*5*) as well as of damage to prefrontal cortex (*23*). The fixed interval (FI) schedule requires the subject to make a

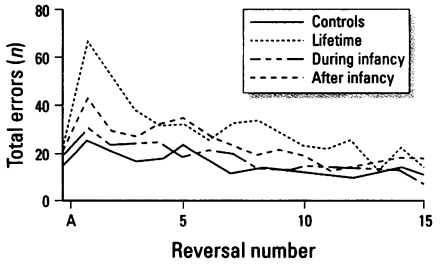

Figure 1. The total number of errors for the initial acquisition (A) and over the course of 15 reversals of a nonspatial discrimination reversal task. Monkeys were dosed with 1,500 µg/kg/day of lead continuously beginning at birth, during infancy only (to 400 days of age), or continuously beginning after infancy (at 300 days of age). Steady-state blood levels during dosing were approximately 20 µg/dL. Testing was performed at about 3 years of age. Data from Rice and Gilbert (*15*).

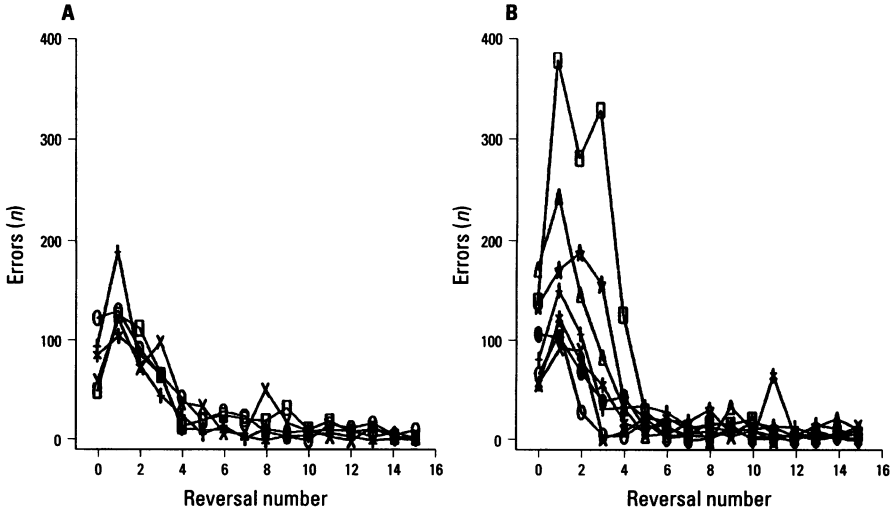

Figure 2. The total number of errors for the initial acquisition (0) and across 15 reversals of a nonspatial discrimination task in monkeys dosed from birth to 20 weeks of age with (*A*) 0 or (*B*) 7.5 µg/kg/day of an environmentally relevant PCB congener mixture. Blood PCB concentrations of treated monkeys at 20 weeks were 1.5–3.0 ppb. Each symbol represents an individual monkey. Data from Rice and Hayward (*16*).

single response after a specified period of time has elapsed, which remains fixed from interval to interval. Similar to the delayed alternation task, there are no external cues to signal progression of the interval or the availability of the opportunity for reinforcement. Therefore, the subject must rely on internal cues to assess the passage of time. Although only one response at the end of the interval is required for reinforcement, FI responding is typically characterized by a gradually accelerating rate of response terminating in reinforcement. Because the rate and pattern of responding are not specified by the schedule, the subject may respond over a wide range of response rates without affecting the density of reinforcement. That is, reinforcers will be delivered at approximately the specified FI value unless the response rate is so low that a significant length of time elapses between the end of the interval and the reinforced response. In general, however, a lower response rate is more efficient than a high rate because fewer responses are emitted for each reinforcer.

Developmental exposure to lead at low to moderate levels results in an increased rate of response on the FI schedule (*12,24*). This is illustrated by the cohort of monkeys in our laboratory, in which groups were exposed from birth onward, during infancy only, or beginning after infancy (*25*). All of the lead-treated groups responded at higher rates than controls over the course of the 30-session (day) experiment (Figure 6). Moreover, the three lead-treated groups were about equally affected, regardless of length of exposure or developmental period during which exposure occurred.

The group of monkeys exposed during infancy to PCBs also exhibited an increased rate of response compared to controls on an FI schedule years after cessation of exposure (*26*) (Figure 7). In addition, the PCB-exposed group exhibited retarded acquisition of terminal FI performance, as evidenced by a slower increase across sessions in the pause at the beginning of the interval, which typically is short (a few seconds) at the beginning of the experiment and increases over successive sessions to a substantial portion of the interval as the monkey learns that reinforcers are not available close together in time. Suboptimal or inefficient performance on an FI schedule may indicate an inability to use internal cues to

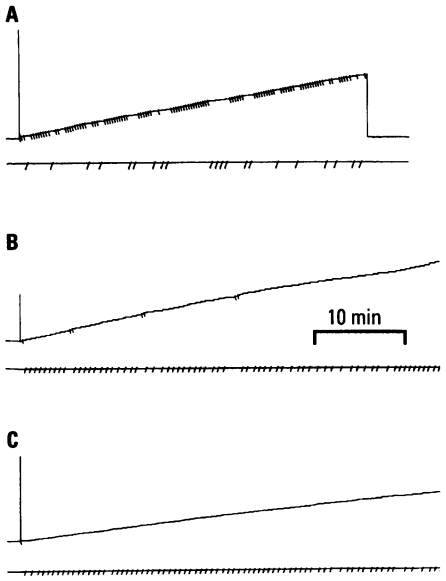

Figure 3. Representative cumulative records of one session of a spatial delayed alternation task for one individual from (*A*) the control group or the groups continuously dosed beginning at birth with (*B*) 50 or (*C*) 100 µg/kg/day of lead. Steady-state blood lead concentrations for both dose groups were approximately 10 µg/dL. For each record, increasing time into the session is indicated from left to right. Each downward deflection of the top pen indicates a correct response and therefore a reinforcer, whereas downward deflection of the bottom pen indicates an incorrect response. Performance by both lead-treated monkeys is characterized by repeatedly responding on the incorrect position for long periods of time. For example, the first response (*C*) was reinforced because the monkey was allowed to respond on either position on the first trial. Thereafter, the monkey continued to respond on the preferred (now incorrect) position for dozens of trials without responding on the nonpreferred position. Only part of the session is depicted. Data from Rice and Karpinski (*21*).

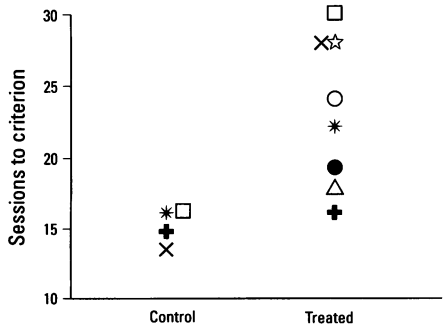

Figure 4. The number of sessions required to learn a spatial delayed alternation task to a predetermined criterion by control and monkeys dosed with a PCB mixture during infancy (see Figure 2). Each symbol represents an individual monkey. Data from Rice and Hayward (*16*).

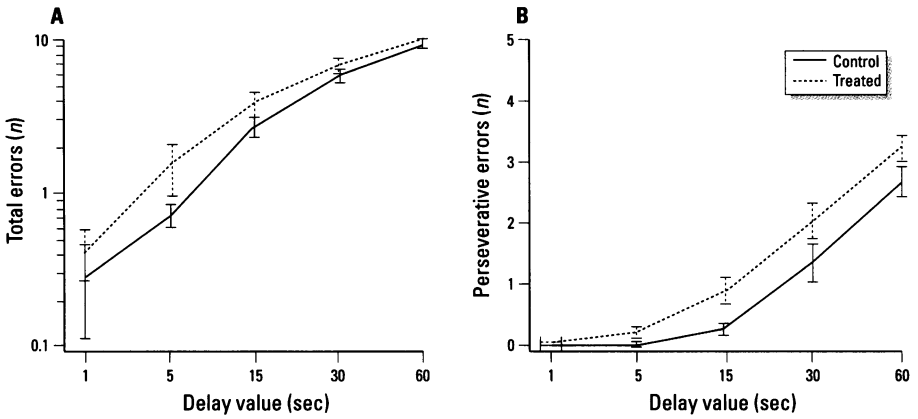

Figure 5. (*A*) The total number of errors and (*B*) the perseverative errors (repeated errors after an initial incorrect response) on a spatial delayed alternation task for control and monkeys treated during infancy with a PCB mixture (see Figure 2). In this phase of the experiment, delay values between 1 and 60 sec were interspersed in a balanced design within each session. Treated monkeys made more perseverative errors but not more total errors than controls during this part of the experiment. Data from Rice and Hayward (*16*).

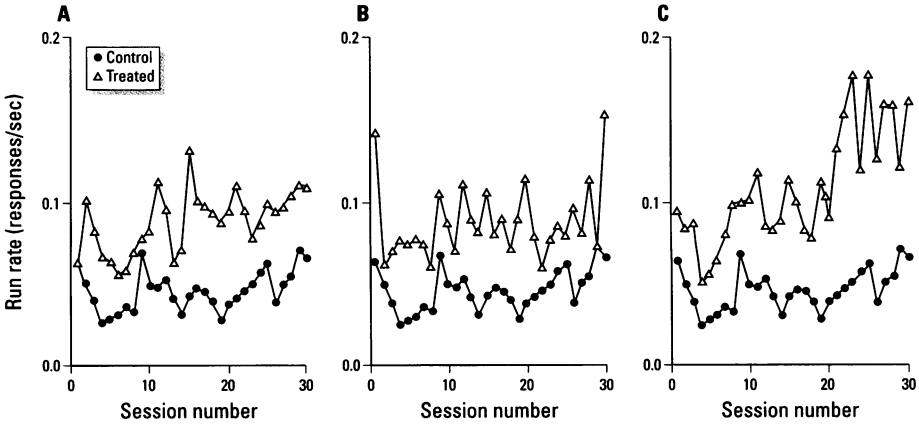

Figure 6. Response rate over 30 sessions on an FI schedule of reinforcement in monkeys exposed (*A*) over the lifetime, (*B*) during infancy only, or (*C*) continuously after infancy compared to controls when tested as adults. All three treated groups responded at a higher rate than controls, resulting in less-efficient performance. Data from Rice (*25*).

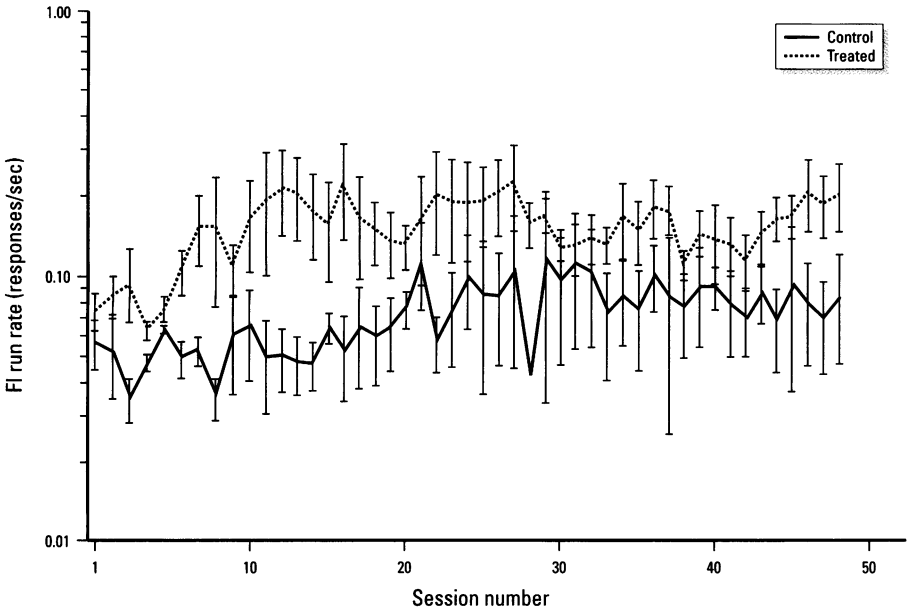

Figure 7. Response rate over 50 sessions of an FI schedule for controls and monkeys exposed to a PCB congener mixture from birth to 20 weeks. PCB-treated monkeys responded at higher rates than controls, resulting in more inefficient performance. Data from Rice (*26*).

organize behavior temporally, an essential skill for the planning or completion of tasks.

Conclusion

Developmental exposure to lead or PCBs results in a pattern of behavioral impairment in monkeys and other animals consistent with some of the features demonstrated by children with ADHD. These include impaired ability to organize behavior temporally and inability to learn from the consequences of previous actions. This is not to suggest that ADHD is caused exclusively by neurotoxic agents in the environment. Genetic and other environmental factors play major roles in the etiology of this disability. However, it seems reasonable to postulate that environmental neurotoxicants contribute to the prevalence of ADHD currently being identified in children; to what degree this may be true is unknown.

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