Age‐related Differences in Distractibility and Response to Methylphenidate in Monkeys

Increased susceptibility to distraction is a symptom of normal aging and several clinical syndromes, including Alzheimer’s disease and attention deficit disorders. In the present study, aged and young adult macaques were well‐trained to perform an automated delayed matching‐to‐sample (DMTS) task which assesses both attention and short‐term memory. On 19% of all trials, a task‐relevant distracting stimulus was presented during either the initial 1 or 3 s of delay intervals (early onset) or the final 1 or 3 s of delay intervals (late onset). In aged monkeys, both early and late onset distractors lasting 1 or 3 s impaired delayed recall on trials with the shortest delay intervals, but did not affect accuracy on trials with long delay intervals. In contrast, young adult monkeys were impaired only by the presence of an early onset distractor lasting 3 s. Impairment was selective for only those trials with the shortest delay intervals. Late onset distractors were relatively ineffective in producing distractibility in young adult animals. Methylphenidate (MPH; 0.005–1.0 mg/kg) failed to reduce distractibility in aged monkeys, producing locomotor abnormalities and hypophagia at doses ranging from 0.25 to 1.0 mg/kg. In young adult monkeys, however, distractibility was significantly attenuated by administration of the 0.125 mg/kg dose. Habituation to the distracting stimulus (under saline conditions) was assessed throughout the study and was not evident at any time point of testing. These data indicate that attention and recall after brief delays are impaired following exposure to a task‐relevant distracting stimulus in both aged and young adult monkeys, but that aged monkeys are more susceptible to distraction and do not receive significant benefit from MPH administration.

Introduction

Impaired attention and susceptibility to distraction are prominent symptoms of normal aging, Alzheimer’s type dementia (ATD) and attention deficit disorder (ADD). Aged humans with no diagnoses of cognitive impairment demonstrate increased susceptibility to distraction by both task‐relevant and irrelevant extraneous stimuli, as compared to young adult subjects (Hoyer et al., 1979; Davis et al., 1990). Similarly, patients with ATD are impaired in their maintenance of attention relative to aged‐matched controls (Broks et al., 1988; Jones et al., 1992). Deficits in sustained attention and susceptibility to distraction are perhaps most prominent in ADD (Elia, 1993). In aged monkeys, delayed recall is impaired if stimuli characterized as irrelevant to the recall task are presented during delay intervals (Bartus and Dean, 1979; Arnsten and Contant, 1992). Similarly, delayed recall without distracting stimuli, which requires the integrity of brief sustained attention and short‐term memory, is also impaired in aged monkeys, as compared to young monkeys (Bartus et al., 1979; Buccafusco and Jackson, 1991; Jackson and Buccafusco, 1991; Terry et al., 1993).

The neurochemical underpinnings of age‐related increases in distractibility, as well as that in patients with ATD and ADD, are likely to involve disruption of catecholamine (CA) systems in the prefrontal association cortex (PFC). Several reports utilizing brain imaging techniques have demonstrated a role for the PFC in the maintenance of attention in humans (Roland, 1982; Pardo et al., 1991). Furthermore, damage to this area is associated with impaired attention and susceptibility to distraction by irrelevant stimuli in humans (Woods and Knight, 1986; Wilkins et al., 1987) and non‐human primates (Bartus and Levere, 1977), as well as closely related cognitive processes involved in working memory (Goldman and Rosvold, 1970; Goldman‐Rakic, 1987). Significant decreases in both noradrenergic and dopaminergic activity in the PFC of aged, cognitively impaired monkeys has been widely documented (Arnsten and Goldman‐Rakic, 1984; Brozoski et al., 1979; Goldman‐Rakic and Brown, 1981). Moreover, α2‐adrenergic agonists such as clonidine and guanfacine improve short‐term memory (Arnsten and Goldman‐Rakic, 1985; Arnsten et al., 1988; Jackson and Buccafusco, 1991) and decrease distractibility in aged monkeys (Arnsten and Contant 1992). At least some of the beneficial effects of α2 agonists on cognition appear to be mediated by receptors of the PFC (Arnsten and Goldman‐Rakic, 1985). Less is known regarding the role of dopaminergic systems in age‐related cognitive decline. However, the dopamine (DA) D2 receptor agonist quinpirole improved short‐term memory in young monkeys performing a delayed recall task (Arnsten et al., 1995). In this study, performance of aged monkeys was not enhanced by quinpirole, a possible consequence of untoward drug effects including agitation and aggression. The D1 receptor partial agonist SKF83859 improved recall in both aged monkeys and reserpinized young monkeys (Arnsten et al., 1994). These same aged monkeys demonstrated an insensitivity to the D1 antagonist SCH23390, relative to young monkeys (Arnsten et al., 1994). Thus, aged monkeys appear to suffer from impairments in CNS DA activity, and loss of function of D1 type receptors may be selectively involved in some of the cognitive deficits observed in these monkeys.

Several studies have confirmed the ability of methylphenidate (MPH), a DA/NE release agonist, to improve attention (e.g. increase target detection, decrease errors of omission) in children diagnosed with ADHD (Charles et al., 1979; Rapport et al., 1993) and in non‐ADD children with mild cognitive deficits (Aman et al., 1991). Young adults with ADD (Spencer et al., 1999) require the integrity of brief sustained attention and short‐term memory (Bartus et al., 1979; Davis et al., 1990). Similarly, delayed recall without distracting stimuli, which requires the integrity of brief sustained attention and short‐term memory, is also impaired in aged monkeys, as compared to young monkeys (Bartus et al., 1979; Buccafusco and Jackson, 1991; Jackson and Buccafusco, 1991; Terry et al., 1993).

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and which, it was hypothesized, would be sensitive to alterations and is not relevant to successful completion of the task, a process young and aged subjects to discern when a familiar stimulus is this paradigm provides an assessment, then, of the ability of both quite intact in young monkeys. The use of task-relevant stimuli in (1979) suggests that the ability to ignore irrelevant stimuli is well as normal aging. However, the work of Bartus and Dean further attending to them, are impaired in both AD and ADD, as

re-establishment of typical baseline performance prior to the onset of this study. The previous pharmacological treatment included short-acting novel agonists of brain nicotinic acetylcholine receptor subtypes which produced no untoward effects on the animals (Buccafusco et al., 1995; Prendergast et al., 1997).

Eight young adult (10–13 years) macaques (three male Macaca nemesstri)na; two female M. nesmestria; two male M. mulatta; and one female M. mulatta) and six aged (>21.5 years) macaques (three male and three female M. mulatta) served as subjects. Monkeys were individually housed at the Animal Behavior Center of the Medical College of Georgia in stainless steel cages composed of multiple 50 × 28 × 26 in. units. Toys and foraging tubes were provided routinely and monkeys were allowed to observe television programs each afternoon after testing to promote psychological well-being. During a test week, monkeys were maintained on a feeding schedule that allowed ~15% of their normal daily food intake to be derived from banana-flavored reinforcement pellets awarded for correct responses during testing. Standard laboratory monkey chow, fresh fruits and vegetables comprised the remainder of their daily food intake. Water was available ad libitum. All procedures employed during this study were reviewed and approved by the Medical College of Georgia Institutional Animal Care and Use Committee and are consistent with AAALAC guidelines.

DMTS Procedure
All monkeys were administered saline or MPH (Sigma Chemicals, St Louis, MO; 0.05–1.0 mg/kg) dissolved in saline in random dose order in the gastrocnemius muscle 10 min prior to testing in a volume of 0.035 ml/kg. Aged monkeys received an additional two doses of MPH (0.01 and 0.005 mg/kg). Doses were chosen to include those previously reported to alter the performance of young and aged monkeys performing standard

Materials and Methods

Subjects
The monkeys employed had previously participated in one or more short-term studies of memory-enhancing agents and were well trained to perform the DMTS task for at least 1 year prior to the beginning of this study. Prior drug experience had produced no untoward effects in the animals, and they were allowed at least a 1 month wash-out period and

1995) and those with no psychiatric diagnoses were also reported to demonstrate enhanced vigilance after administration of 20 mg of MPH (Camp-Bruno and Herting, 1994). Furthermore, short-term memory, as assessed by delayed recall, was enhanced in each of these subject samples, as a likely consequence of improved attention during initial stimulus presentation (Aman et al., 1991; Rapport et al., 1993; Camp-Bruno and Herting, 1994). In animal models, MPH was shown to enhance variable-interval responding for a weak reinforcer in normal rats (Heyman, 1992) and fixed-interval responding in a putative rat model of ADHD, the spontaneously hypertensive rat (Sagvolden et al., 1992). Schneider et al. (1993) have demonstrated the ability of MPH to reduce errors of omission in delayed recall, a common feature of ADD, in young adult monkeys pretreated with the dopaminergic neurotoxin MPTP. Clinically, the preferred pharmacological treatment of ADD with hyperactivity in children is MPH (Klein et al., 1980; Elia, 1993). Further, the α2 agonist clonidine has proven efficacious in decreasing distractibility in ADD children (Hunt et al., 1985; Fox and Reider, 1993). As a whole, these data implicate a significant role for CNS CA activity in the maintenance of attention.

The purpose of the present study was to assess the ability of a task-relevant distractor stimulus interposed between sample and choice presentations to impair delayed recall in aged and young adult monkeys performing an automated version of the delayed matching-to-sample (DMTS) task, the completion of which is largely dependent upon activity of the PFC. Several investigations have characterized the distracting effects of irrelevant stimuli in both humans and aged primates (Bartus and Dean, 1979; Hoyer et al., 1979; Arnsten and Contant, 1992) and some have shown that disruptive effects of distractors can be reduced by CA agonists. However, Bartus and Dean (1979) reported that young monkeys were unaffected by exposure to an irrelevant stimulus. Thus, distractibility is enhanced during normal, as well as pathological, aging.

It has not been determined whether stimuli that possess task-relevant properties produce significant disruption of attention and/or memory required for recall after brief delays in aged and young adult monkeys and if this distraction may be reduced by administration of a CA agonist. Identification of the information provided by such stimuli as being of no utility in task performance may represent a cognitive process of greater complexity than that of ignoring irrelevant stimuli. Clearly, the initial attentive processes involved in perceiving irrelevant stimuli, judging their utility as a source of information, and further attending to them, are impaired in both AD and ADD, as well as normal aging. However, the work of Bartus and Dean (1979) suggests that the ability to ignore irrelevant stimuli is quite intact in young monkeys. The use of task-relevant stimuli in this paradigm provides an assessment, then, of the ability of both young and aged subjects to discern when a familiar stimulus is and is not relevant to successful completion of the task, a process which would appear to be of considerable cognitive complexity and which, it was hypothesized, would be sensitive to alterations in CA activity.

Figure 1. Schematic representation of a monkey performing an automated DMTS trial during which an early-onset distractor is presented. Arrows indicate the temporal progression of a trial and associated changes in illumination of lights behind sample and choice push-keys.
delayed-recall tasks (Bartus, 1979; Schneider et al., 1994). For DMTS testing, test panels were attached to the home cages. Stimuli on the test panels were 2.54 cm diameter colored disks (red, yellow or green) presented by light-emitting diodes located behind clear plastic push-keys. A trial began with the illumination of the sample key by one of the colored disks. The sample light remained lit until the sample key was depressed by an animal, initiating one of four pre-programmed delay intervals, during which no disks were illuminated. Following the delay interval, two choice lights located below the sample key were illuminated. One of the choice lights matched the color of the sample light. These disks remained illuminated until a monkey pressed one of the two lit keys. Key-presses of choice stimuli which matched the color of the sample stimulus were rewarded by a 300 mg banana-flavored pellet. Non-matching choices were neither rewarded nor punished. Matching configurations were fully counterbalanced for side, delay and hue. A new trial was initiated 5 s after the second key-press on a preceding trial. Monkeys completed 96 trials on each day of testing.

Four possible delay intervals between a monkey’s response to the sample light and the presentation of the two choice lights were employed: zero delay and short, medium and long delays. Short, medium and long delay intervals were individually adjusted to produce stable performance levels approximating the following levels of accuracy: short (<75–85% correct), medium (65–75% correct) and long (55–65% correct). The monkeys’ performance for zero delay trials averaged 85–100% correct.

**Distractor Stimulus**

Test sessions with distractors (termed ‘interference sessions’; Arnsten and Contant, 1992) were conducted twice each week with a minimum of 3 days of standard DMTS testing conducted between each session. To examine the extent to which habituation to the distractors may have developed during repeated testing with different doses of MPH, interference sessions were conducted under saline conditions after administration of the initial two doses of MPH and again after administration of the last dose of MPH.

A schematic representation of a trial completed during interferences sessions is presented in Figure 1. On 18 of the 96 trials completed during test sessions, distractor stimuli were presented. The stimuli were presented simultaneously on the sample and choice keys for 3 s and consist of a random pattern of the three colored lights flashing in an alternating manner. The distractor lights were comprised of the same three colors used for sample and choice stimuli presentation. The total duration of illumination for a given colored light was 0.33 s. Immediately as one colored light was extinguished, a different colored light was presented in random order. Each color is presented in random order on each key once during a 1 s distractor and three times during a 3 s distractor.

Distractor stimuli were present an equal number of times in trials with short, medium and long delay intervals. The remaining trials were completed with no delay interval or distractor and were randomly placed throughout the test session. Initially, the onset of the distractor stimuli (either 1 or 3 s in duration) began either 1 s after depression of the sample key (‘early onset distractor’), or 1 or 3 s prior to the end of each delay interval (‘late onset distractor’). Given the short duration of many delay intervals for aged monkeys, there were most likely little differences between early or late-onset distractors lasting 1 or 3 s. For example, the mean duration of short delays for aged animals was 4.38 ± 0.71 s. Thus, both a 1 and 3 s distractor, presented either early or late during these delay intervals, would occupy all or most of the delay interval. For this reason, it was not expected that response on short delay trials would be markedly different for different distractors in aged monkeys.

For interference sessions completed after MPH administration, all distractors began 1 s after depression of the sample key and lasted for 3 s. The following parameters were recorded during all test sessions: percentage correct on distractor and non-distractor trials with short, medium and long delay intervals, and latency of response to sample and choice stimuli.

**Statistics**

Two-way, repeated-measures analyses of variance were used to compare DMTS accuracy on short, medium and long delay distractor and non-distractor trials during interference sessions to accuracy on trials completed during standard DMTS testing (saline-control data for standard DMTS testing were obtained each Monday). Accuracy on distractor and non-distractor trials completed after administration of saline and doses of MPH was compared to like trials completed after saline during standard DMTS testing. In addition, these analyses were employed to compare the response of both aged and non-aged monkeys to distractor stimuli lasting 1 and 3 s. Data derived from trials completed after administration of the 1.0 mg/kg dose of MPH were not included in analyses because of the presence of overt toxicity (described below) in both aged and young adult
monkeys. As a result, not all monkeys in each group were administered this dose of MPH.

Results

Early-onset Distractor

Aged Monkeys

The duration of short, medium and long delays for aged monkeys averaged 4.38 ± 0.71, 12.25 ± 4.18 and 23.38 ± 8.58 s respectively. Baseline performance on trials with these delay intervals during standard DMTS testing (after saline administration) was 80.10 ± 3.24, 65.70 ± 3.73 and 53.7 ± 2.02% correct respectively. Baseline accuracy on trials with no delay intervals (zero delay) averaged 93.5 ± 2.7% correct. Exposure to a distractor stimulus lasting 1 s immediately after depression of the sample key resulted in a significant decrement in DMTS performance (Fig. 2; main effect for distractor \( F(2,32) = 3.69, P < 0.05 \)). Post hoc (Newman–Keuls) comparisons indicated a significant difference between distractor trials and trials completed during standard DMTS testing (\( P < 0.05 \)). Upon visual inspection of the data, the effect is almost solely attributable to a decrease in performance on short delay trials (62.5 ± 4.87 vs. 80.10 ± 3.24% correct on distractor and baseline short delay trials respectively). Accuracy on medium and long delay trials was largely unaffected by the presence of a distractor during the delay interval with changes from baseline accuracy of only -0.40 and -3.70% correct on these trials respectively. Similarly, performance on trials with no delay intervals was also not altered by distractor presentation. Performance on non-distractor trials completed during interference sessions was not impaired (Fig. 2).

Young Adult Monkeys

The duration of short, medium and long delays for the eight young adult monkeys averaged 11.2 ± 2.20, 52.50 ± 8.54 and 98.30 ± 17.21 s respectively. At each interval, these delays were considerably longer than those of aged monkeys. Baseline performance on trials with these delays during standard DMTS testing was 85.40 ± 1.21, 68.80 ± 2.69 and 59.40 ± 2.63% correct respectively. Accuracy on zero delay trials averaged 95.8 ± 2.15% correct. Given that different macaques were employed in this group, baseline distractor performance (3 s) of rhesus and pigtail monkeys was compared to assure that there was no difference in the distractibility of different species. A two-way, repeated-measures ANOVA indicated that rhesus and pigtail monkeys responded in nearly identical manners to this stimulus (species × delay interaction: \( P = 0.83 \)). Exposure to a distractor stimulus lasting 1 s resulted in the following levels of performance on short, medium and long delay trials: 77.50 ± 2.50, 67.50 ± 9.35 and 47.5 ± 9.19% respectively. DMTS accuracy on these trials was not significantly impaired by presentation of this distractor. Similarly, accuracy on non-distractor trials completed during interference sessions was not impaired (Fig. 2). Performance on trials with no delays was also not altered by distractor presentation. Presentation of a distractor stimulus lasting 3 s did produce an impairment of DMTS accuracy [interaction of delay × presence/absence of distractor = \( F(2,14) = 3.55, P < 0.05 \)]. This impairment was observed only on trials with short delay intervals, wherein group accuracy was decreased by 21.90% (Newman–Keuls post hoc = \( P < 0.05 \)). Trials with medium and long delay intervals were not significantly impaired by the presence of...
the 3 s distractor. In addition, non-distractor trials were not significantly altered by the presence of this distractor.

The performance of aged and non-aged monkeys following exposure to a distractor (1 or 3 s) after saline administration was compared in a separate analysis. The interaction term analyzing age and distractor influences approached statistical significance ($P < 0.08$). Thus, while it is evident that aged monkeys were more impaired by exposure to the distractor (1 s, in particular), some variability was noted and probably precluded statistical significance.

**Late-onset Distractor**

**Aged Monkeys**
To examine the relative influence of the placement of a distractor within the delay interval on distractibility, all monkeys were administered separate interference sessions during which distractors of 1 or 3 s in duration were presented immediately prior (either 1 or 3 s prior) to the end of delay intervals (again on 19% of all trials). As indicated in Figure 2, baseline performance of aged monkeys on short delay trials (85.4 ± 1.79% correct) was impaired by presentation of this late-onset distractor lasting 1 s (68.8 ± 5.35% correct). This impairment approached statistical significance (main effect for distractor = $P < 0.07$) but was not as pronounced as was that observed following presentation of a 1 s distractor immediately after depression of the sample key (Fig. 2). Accuracy on zero delay trials was not impaired following exposure to this distractor.

Following presentation of a late onset distractor lasting 3 s, accuracy on short delay trials was markedly impaired relative to baseline performance levels (57.1 ± 5.36 vs. 84.5 ± 1.75% correct respectively; Fig. 2). This impairment was selective for those trials with the shortest delay intervals; trials with medium and long delay intervals were not significantly impaired by presentation of this distractor [delay × distractor interaction: $F(4,24) = 3.08, P < 0.05$]. The percentage of correct responses on non-distractor trials with short delay intervals was reduced on average following presentation of this distractor (to 71.4 ± 4.55% correct), though this effect was not statistically significant. Zero delay trial accuracy was not altered by distractor presentation. Further, performance on medium delay trials, which was dramatically impaired after exposure to a 3 s distractor early in the delay interval, was unaffected by presentation of a late onset 3 s distractor (only ~4.30% vs. baseline).

**Young Adult Monkeys**
In young adult monkeys, DMTS accuracy was not markedly impaired by presentation of a late onset distractor lasting 1 s (Fig. 3). Significant variability was noted, however, with one monkey (no. 13) performing at levels of 50 and 12.5% correct on short and medium delay trials respectively, following exposure to this distractor. This same monkey obtained only 31.3% correct on short delay non-distractor trials completed during this interference session, which contributed to the reduction in the group mean to 71.9 ± 7.18% correct. Performance of non-distractor and zero delay trials was not significantly disrupted by exposure to this distractor.

The average short delay interval in this sample of young monkeys was 11.2 ± 2.2 s and it was observed by experimenters that many of these monkeys were not attending to the test panels during the latter stages of these delay periods. This may well account for our finding that exposure to a 3 s late onset distractor did not significantly impair DMTS performance; although a reduction in performance was noted (70.3 ± 7.81 vs. 83.3 ± 2.49% correct for controls), it was associated with considerable variability. Similarly, non-distractor trials associated with this interference session were not significantly impaired though considerable variability was again noted.

A comparison of the impairment produced by exposure to late onset distractors lasting 1 or 3 s did not yield statistical significance (interaction of age and distractor, $P > 0.11$). While there does appear to be a greater sensitivity of aged animals to the disruptive effects of these distractors based on inspection of the data, the variability in responding likely contributed to the failure to achieve statistical significance.

Figure 4. In five aged monkeys, MPH administration (0.005–1.0 mg/kg) did not reduce distractibility produced by exposure to an early onset distractor lasting 3 s. Accuracy on trials with medium and long delay intervals was also not affected by MPH administration. *$P < 0.05$ vs. baseline performance.
**MPH Administration**

Given our previous finding that presentation of a distractor stimulus at the end of a given delay interval resulted in a less pronounced impairment of short delay performance than did a distractor presented immediately after sample key depression, an early onset distractor was used to assess the ability of MPH to reduce distractibility. Both aged and young monkeys were presented with a 3 s distractor, the only duration of distractor which impaired accuracy in both groups, immediately after depression of the sample stimulus key as previously described.

**Aged Monkeys**

As was demonstrated during initial testing, presentation of a 3 s distractor resulted in an impairment of accuracy on short delay trials conducted during interference sessions [main effect for distractor, Newman–Keuls post hoc: F(4,32) = 3.74, P < 0.05]. Administration of MPH did not reverse this distractibility (Fig. 4). On saline non-distractor trials, short delay accuracy was reduced to 55.0 ± 8.48% correct (vs. 85.4 ± 1.79% correct for baseline data). Accuracy on medium delay trials was not significantly impaired by presentation of the distractor, though saline-distractor performance was less accurate than baseline performance. On short delay trial trials, accuracy remained impaired relative to baseline after administration of each dose of MPH (P < 0.05). Accuracy on trials with no delays (zero delay trials) was not altered by distractor presentation (P = 0.68) or MPH administration and ranged from 80 to 89% during the course of the study.

A probable cause of the excessive variability observed in these monkeys following MPH administration is drug-induced behavioral toxicity. Following administration of the 0.25 mg/kg dose, all monkeys completed testing with no overt signs of toxicity. However, two of these aged monkeys failed to complete all DMTS trials 24 h after drug administration, suggesting the possibility of a protracted drug-induced toxicity. After administration of the 1.0 mg/kg dose, only one monkey completed all 96 total DMTS trials and remained primarily immobile in the bottom of the cage for the following 4–5 h. Two other monkeys finished testing after administration of this dose, but did not eat for the following 24 h and both remained largely immobile at the bottom of their cages for 4–5 h. One of these monkeys displayed marked hypophagia for ~3 full days after administration of the 1.0 mg/kg dose. However, it is unclear if this protracted hypophagia reflects systemic toxicity or an anorectic effect.

**Sample/Choice Latencies**

Two measures of response latency were also recorded during DMTS testing conducted after MPH administration: choice latency, the time interval between presentation of the two choice stimuli and depression of one of the choice keys; and sample latency, the time interval between initiation of a new trial (illumination of the stimulus light behind the sample key) and depression of the sample key by the monkeys. Latency data were analyzed for both correctly and incorrectly completed trials following administration of each dose of MPH.

**Young Adult Monkeys**

In young adult monkeys, exposure to a 3 s distractor resulted in a significant decrement in DMTS accuracy on short delay trials [-28.6% correct vs. baseline; F(2,60) = 6.47, P < 0.01]. Non-distractor trials were unaffected by this exposure (data not shown). However, distractibility was significantly attenuated by administration of the 0.125 mg/kg dose of MPH (Fig. 5; post hoc = P < 0.05 vs. saline-distractor trials). On distractor trials, DMTS accuracy for short delay trials was increased following administration of this dose to 71.88 ± 3.45% correct (vs. 54.69 ± 8.64% for saline-distractor trials). While this represents a considerable benefit above saline-distractor levels of performance, baseline levels of accuracy were not achieved, though performance associated with this dose of MPH was not significantly different from baseline. Performance on medium and long delay trials was unaffected by distractor exposure and was not altered by administration of MPH at any dose. As in aged monkeys, accuracy on zero delay trials was unaffected by distractor present-
Young Adult Monkeys
Following administration of saline, sample and choice latencies on correctly completed trials averaged 1.38 ± 0.2 and 3.11 ± 0.81 s respectively. As with aged monkeys, these latencies were not significantly altered by administration of MPH at any dose. For incorrect trials, sample and choice latencies following saline administration averaged 1.31 ± 0.21 and 2.91 ± 0.74 s respectively. These latencies were also unaffected by MPH administration.

Discussion
Impaired cognitive function is often associated with normal aging, ATD and ADD (Hoyer et al., 1979; Davis et al., 1990; Jones et al., 1992). This impairment appears to be due, in large part, to the inability to ignore distracting environmental stimuli and may contribute to deficits in short-term memory. Typically, distracting stimuli that are not relevant to a given task are characterized as being more detrimental to attention than are putative distracting stimuli that share some properties with task cue stimuli (Davis et al., 1990). However, it is likely that both types of extraneous stimuli have considerable influence on distractibility. Previous studies that have examined attention and distractibility in humans have employed distracting stimuli that are both similar to standard test stimuli (task relevant) and some which are dissimilar to test stimuli (task irrelevant). Aged humans are markedly impaired in their ability to perform tasks that require attentional vigilance (i.e. Stroop interference test, DMTS) following exposure to both types of distracting stimuli (Hoyer et al., 1979; Davis et al., 1990). Studies employing similar paradigms with non-human primates have reported enhanced distractibility during delayed recall tasks in aged animals, compared to young animals, following exposure to ‘irrelevant’ stimuli (Bartus and Dean 1979; Arnsten and Contant, 1992).

Initial Distractor Testing
The present data are consistent with the hypothesis that presentation of a task-relevant distractor stimulus impaired DMTS accuracy in both aged and young adult monkeys. That this impairment may reflect a detriment to attention and/or very brief memory is suggested by our finding that it was selective for those trials with the shortest delay intervals, those requiring the least extended memory of stimuli, in both age groups of monkeys. Accuracy of recall on trials with the longest delay intervals was not significantly impaired by presentation of a distractor of either 1 or 3 s in either sample of monkeys. Accuracy of recall on trials with the longest delay intervals was not significantly impaired by presentation of a distractor of either 1 or 3 s in either sample of monkeys. This apparent lack of distractibility may be a consequence of low baseline accuracy on these trials (i.e. a ‘floor’ effect). Accuracy on these trials averaged 59.40 ± 2.63% correct. Therefore, decrements in performance induced by exposure to distractors may have been difficult to detect, if present. Alternatively, these data may suggest that the distractor produces a retroactive interference which persists for only a short duration.

Previous reports of distractibility in monkeys have failed to identify a pattern of delay-selective impairment. Arnsten and Contant (1992) reported impaired accuracy of recall on trials with both short and long delay intervals. However, long delay intervals in that study were chosen such that reliance on short-term memory would be minimized and extended to only 12 s (vs. 23 s in the present study). Thus, it is likely that performance at each delay interval was disproportionately dependent upon the integrity of brief memory and/or attention, whereas long delay accuracy in the present study was largely dependent upon more extended retention of sample stimulus characteristics. The distraction induced by exposure to the random light pattern appears to have decayed prior to the end of long delay intervals for most, if not all monkeys.

As in previous studies conducted in humans (Hoyer et al., 1979; Davis et al., 1990) and monkeys (Bartus and Dean, 1979) susceptibility to distraction in our monkeys was shown to be greater in aged subjects, compared to young adult subjects. Further, aged monkeys were impaired, relative to young adult animals, in their ability to recall stimuli over extended periods of time in that the longest delay intervals performed at above-chance levels averaged 23 s (vs. 98 s in young adult monkeys). Both forms of cognitive deficit are likely to be associated with marked and age-related CA deficits in the PFC. In aged monkeys, an early-onset distractor lasting 1 s markedly impaired accuracy on trials with short delays. This short duration distractor did not impair accuracy on any trials completed by young adult monkeys. Further, an early-onset distractor lasting 3 s similarly impaired short delay accuracy and also impaired performance on trials with medium length delay (which averaged 12.25 ± 4.18 s). It is relevant that the mean length of medium delay trials in these monkeys is nearly identical to that for long delay trials reported by Arnsten and Contant (1992).

Significantly, the performance of aged monkeys on trials without distractors which were completed during interference sessions were also impaired by exposure to a 3 s distractor, though on trials with short delays only. While the reason for this impairment on non-distractor trials is unclear, it may reflect an expectation of distractor presentation or possibly proactive interference. However, performance on subsequent days of testing (using a standard DMTS procedure) was not impaired, suggesting the absence of a lasting interference. A similar effect on non-distractor trials was observed by Arnsten and Contant (1992). In young adult monkeys, exposure to a 3 s early-onset distractor did impair performance on trials with short delays, though no effect on medium delay trials or non-distractor trials was observed. Therefore, while these monkeys are clearly more resistant to distraction than are aged animals, they are susceptible to distraction produced by a relatively brief increase in the duration of distractor exposure. An additional pertinent finding was that, in both aged and young adult monkeys, disposition of distractors (either 1 or 3 s in duration) in the final 1 or 3 s of a given delay did not impair recall to the extent that early-onset distractors did. While aged monkeys were somewhat affected by both 1 and 3 s late-onset distractors, considerable variability was noted and no effect on medium delay trials and/or non-distractor trials was noted. In young adult animals, exposure to neither of the late-onset distractors impaired recall. In both groups of animals, it is likely that some monkeys, those with longer medium and long delay trials, did not observe the late-onset distractors. During these intervals, some monkeys did not appear to be attending to the test panels for extended periods of time after sample key depression. Thus, a distracting effect of late-onset distractors would not be expected. However, time spent in front of the panels was not quantified and not all monkeys were observed. In addition, for both groups of animals latencies to press a choice key typically occurred in 2 s or less, suggesting that monkeys were attending to test panels during the late phases of delay intervals.

MPH and Distractibility
In the present study, aged monkeys appeared to receive little or no benefit in terms of reduced distractibility from MPH admin-
istration. However, it must be noted that the 0.01 mg/kg dose may have attenuated a non-significant impairment produced by distractors observed on trials with medium delay intervals. Impairment observed on short delay trials was not prevented by MPH administration. In addition, upon inspection of performance data associated with each dose of MPH, individual monkeys did not appear to receive benefit from any particular dose of MPH (i.e. most monkeys were ‘non-responders’ to all doses). In fact, with some doses individual monkeys performed the task at levels of accuracy well below their own baseline performance, suggesting some sensitivity to possible toxic effects of MPH, like those (e.g. lethargy and hypophagia) observed after administration of the 0.25 and 1.0 mg/kg doses. Toxicity to MPH was not reflected in altered response latencies following administration of any dose. Further, the most evident symptom of toxicity in these monkeys was lethargy. Thus, toxicity was probably associated with a drug-induced state other than psychomotor agitation. Bartus (1979) reported similar findings with aged monkeys in that MPH (0.1–0.8 mg/kg) afforded no benefit to delayed recall and even impaired recall at higher doses.

MPH has not been found to be efficacious in the treatment of cognitive impairment in ATD patients (see Goodnick and Gershon, 1984), though one uncontrolled, open study did report limited benefit to some patients (Reisberg et al., 1980). In these studies, doses of 20–30 mg were associated with side effects including nervousness, insomnia and anorexia. MPH has, however, shown efficacy in enhancing attention in non-elderly adults and demonstrated a relatively mild profile of side effects (Spencer et al., 1995). The present data are consistent, then, with evidence that the use of MPH and similar agents in elderly patients may be associated with considerable side effects which will preclude therapeutic benefit. Even in those animals which did not show overt aversive effects in this study, distractibility was not, however, reduced.

DMTS accuracy on short delay trials was impaired in the young adult monkeys employed in this study only following exposure to a 3 s early onset distractor stimulus. In contrast to the aged monkeys, these animals received considerable benefit (reduced distractibility) from administration of MPH, particularly the 0.125 mg/kg dose. Although DMTS accuracy on short delay distractor trials did not achieve baseline levels after administration of this dose, accuracy was enhanced well above saline-distractor levels and was not statistically different from baseline levels of accuracy for this delay. The use of MPH to treat attention deficits and enhance attention in non-impaired children, adolescents and non-elderly adults is well documented (Charles et al., 1979; Aman et al., 1991; Rapport et al., 1993) and the present data are consistent with a role for MPH in decreasing distractibility in young adult subjects. However, Bartus (1979) reported that MPH administration in young monkeys was associated only with decrements in delayed recall. This apparent discrepancy may be related to the difference in methods employed.

Saline-distractor interference sessions were conducted on two occasions interspersed between doses of MPH, and for each session distractibility on short delay trials was observed, demonstrating the resistance of this distractor stimulus to habituation. Further, short delay accuracy was not enhanced, relative to saline-distractor levels, following administration of MPH doses other than the 0.125 mg/kg dose. Therefore, the decreased distractibility observed may not be attributed to habituation to the distractor stimulus. Arnsten and Contant (1992) employed task-irrelevant distractor stimuli which initially produced a marked impairment of DMTS accuracy but which also were susceptible to habituation. Thus, the resistance to habituation observed in the present study may be a consequence of the similarity of the distracting stimulus to sample and choice cues.

The beneficial effect of MPH on distractibility/attention is likely to be associated with enhanced CNS CA release, particularly in the PFC. Several researchers have reported evidence of decreases in noradrenergic and dopaminergic activity in the PFC of cognitively impaired monkeys (Goldman-Rakic and Brown, 1981; Arnsten and Goldman-Rakic, 1984). Ongoing activity of PFC neurons undoubtedly contributes to the maintenance of attention and the integrity of memory in both humans (Roland, 1982; Pardo et al., 1991) and non-human primates (Bartus and Levere, 1977; Goldman-Rakic, 1987), and the beneficial effects of the α2-adrenergic agonists clonidine and guanfacine on the maintenance of attention are attributed largely to enhanced adrenergic activity in the PFC (Arnsten and Contant, 1992). Thus, the decreased distractibility observed after MPH administration may be attributed, in part, to increased CA release in the PFC. Other CNS regions likely to be involved in this beneficial effect of MPH include the locus coeruleus and the ascending dorsal bundle which contains noradrenergic processes projecting to the forebrain (Mason and Fibiger, 1978). In addition, striatal abnormalities probably exist in children with ADHD (Costellanos et al., 1994); thus increased CA release in striatal neurons may provide some benefit to cognitive function. Furthermore, cholinergic nuclei such as the nucleus basalis of Meynert undergo significant degeneration in ATD and, possibly, normal aging, and probably contribute to impaired attention in these patients (Arendt et al., 1985).

In sum, these data indicate that exposure to unexpected stimuli during brief delay intervals impairs recall of sample stimuli in both aged and young adult monkeys. In this regard, aged monkeys were more susceptible to the distracting effects of such exposure than are young adult animals. Further, distractibility in young adult monkeys was reduced by administration of MPH, whereas impairment in aged monkeys was not affected by drug administration, possibly as a result of drug-induced untoward effects. As a whole, these data suggest that the model of distractibility employed may be useful in examining mechanisms associated with age-related decrements in cognitive function.

Notes
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