Relationships among cognitive function, fine motor speed and age in the rhesus monkey

Agnès Lacreuse · Paola M. Espinosa ·
James G. Herndon

Received: 6 September 2006 / Revised: 5 October 2006 / Accepted: 5 October 2006 / Published online: 30 November 2006
© American Aging Association 2006

Abstract Declines in fine motor skills and cognitive function are well known features of human aging. Yet, the relationship between age-related impairments in motor and cognitive function remains unclear. Rhesus monkeys, like humans, show marked decline in cognitive and fine motor function with age and are excellent models to investigate potential interactions between age-related declines in cognitive and motor functioning. We investigated the relationships among cognition, motor function and age in 30 male and female rhesus monkeys, 5–28 years of age, tested on a battery of cognitive tasks [acquisition of the delayed non-matching-to-sample (DNMS), DNMS-120s, DNMS-600s, acquisition of delayed recognition span test (DRST), spatial-DRST and object-DRST] and a fine motor task (Lifesaver test). Global cognitive ability, as assessed by the cognitive performance index (CPI), was impaired with age in both sexes, while age-related motor slowing was found only in males. After age was controlled for, half the variance in CPI was predicted by motor speed, with better

cognitive ability associated with slower motor skills. Analyses at the level of each cognitive task revealed that motor speed and age predicted the rate of acquisition of the DNMS. This relationship was robust in males and absent in females. Motor speed was not a significant predictor of any other cognitive variable. We conclude that the relationship between cognition and motor function (1) may be limited to non-spatial tasks; (2) exists independently of age; (3) may reflect different contributions of the fronto-striatal system; (4) may be particularly evident in males.

Key words aging · learning · macaque · motor skills · memory · sex differences

Introduction

In humans cognitive and motor functions deteriorate significantly with age. Age-related cognitive deficits encompass multiple domains, including attention, memory, reasoning, and executive function (Craik and Salthouse 2000; Park and Schwartz 2000). Age-related motor impairments are also ubiquitous, with deficits in speed and accuracy evident in the planning, the execution and the control of movement (Krampe 2002; Spirduso and MacRae 1990). Many studies of elderly humans have shown a relationship between motor functioning and cognitive status. For example, Camicioli et al. (1998) reported that motor slowing (finger tapping, coordination and walking) preceded

---

A. Lacreuse · P. M. Espinosa · J. G. Herndon
Division of Neuroscience, Yerkes National Primate
Research Center, Emory University,
Atlanta, GA 30322, USA

A. Lacreuse (✉)
Department of Psychology, University of Massachusetts—
Amherst, Tobin Hall, 135 Hicks Way,
Amherst, MA 01003, USA
e-mail: alacreuse@psych.umass.edu

cognitive impairment in a cohort of very old adults. In another study the severity of deficits in tasks of complex motor function differentiated healthy elderly from patients with mild cognitive impairment and patients with Alzheimer's disease (Kluger et al. 1997). Relationships between age-related declines in motor performance and some aspects of cognitive function were also noted in a pursuit rotor learning task, in which poor motor performance was associated with low scores on non-verbal working memory (Raz et al. 2000). It has been suggested that the association between cognitive and sensorimotor functioning increases with age (Li and Lindenberger 2002; Li et al. 2001). Combined declines in cognitive and motor processes with age could be due to declining dopaminergic function. Indeed, the nigrostriatal dopaminergic system plays a major role in the control of both cognitive and motor processes (Nieoullon and Coquerel 2003), and its deterioration with aging has been implicated in an array of cognitive (Arnsten and Goldman-Rakic 1985; Arnsten et al. 1994; Moore et al. 2005; Reeves 2005; Reeves et al. 2002) and motor deficits (Emborg and Kordower 2002; Grondin et al. 2000; Irwin et al. 1994). Volkow et al. (1998) provided support for this hypothesis, by showing that D2 receptor availability in the caudate and putamen in healthy elderly subjects was positively correlated with performance on a finger tapping task and performance on specific cognitive tasks dependent on frontal function.

In sharp contrast with these findings in humans, several studies using rodent models have suggested that age-related deficits in learning and memory are independent of the motor deficits that develop with age (Gage et al. 1989; Gallagher and Burwell 1989; Miyagawa et al. 1998; Rapp et al. 1987) but see Chen et al. (2004). The source of these discrepancies between the human and rodent literature is unclear but may be related to differences in the assessment of motor function between the two species, with human motor function typically measured by some aspects of manual ability (finger tapping, mirror tracing, peg-board tests), while motor function is typically assessed through gross locomotor skills in rodents. In addition, discrepancies may also arise from the selection of different cognitive domains in humans and rodents, as rodent studies have almost exclusively tapped spatial abilities, while human studies usually examine a variety of cognitive domains.

The goal of the present study was to clarify the relationships between age-related declines in cognitive function and fine motor ability in the rhesus monkey, a model of human aging, which is very similar to humans in terms of the cognitive deficits (Gallagher and Rapp 1997; Herndon and Lacreux 2002; Roberts 2002; Voytko 1998) and fine motor impairments (Zhang et al. 2000) that develop with age. We tested the hypothesis that age-related cognitive impairment is associated with slowing of fine motor ability in the rhesus monkey.

Methods

Subjects

We analyzed cognitive performance and fine motor skills of 30 rhesus monkeys (*Macaca mulatta*), including 20 monkeys tested for motor function as part of a previous study (Lacreux et al. 2005). All monkeys were tested by the same procedure. As can be seen in Table 1, the group comprised 13 females and 17 males, aged 4 years to 28 years old (mean = 16.6, SD=7.2). Age was not significantly different between young males (mean=5.66, SD=0.88) and young females (mean = 7.19, SD=1.78; $t(7)=3.20$, ns) or old males (mean=20.95, SD=3.11) and old females (mean = 20.05, SD=2.39, $t(19)=1.27$, ns). The monkeys were not deprived of food or water, and they received their normal daily ration of monkey chow and fresh fruits. They were humanely treated in accordance with the standards of the Association for Assessment and Accreditation of Laboratory Animal Care, International.

Procedure

Cognitive tasks

Each monkey was first tested on a battery of cognitive tasks, described elsewhere in detail (Herndon et al. 1997) and briefly summarized here. Testing on the cognitive tasks took place in a Wisconsin general testing apparatus (WGTA). In the WGTA the experimenter sat behind a one-way screen facing a test board containing three wells that could be baited with food. Between trials, the test board was concealed from the monkey by an opaque screen. Monkeys were presented

Table 1 Code, sex, age in years, motor speed (s) and cognitive performance index (CPI) of the 30 rhesus monkeys.

Monkey's code	Sex	Age at cognitive assessment (years)	Motor speed (s)	Cognitive performance index (CPI)
RYi6	F	7.52	2.00	1.34
RUf4*	F	8.78	4.26	−0.71
RQb6*	F	9.27	2.36	0.90
Rod2	F	17.42	3.61	0.92
N817*	F	18.27	2.81	0.36
N851*	F	18.29	3.82	−0.27
Rod1	F	18.83	4.22	−1.32
N710*	F	18.84	1.46	−4.47
N764*	F	19.23	2.93	−1.04
RTv*	F	20.61	2.05	−0.64
REy*	F	20.79	3.03	−0.25
RDv	F	23.71	1.73	−4.20
RLt	F	24.56	3.35	−0.69
RYj6*	M	4.52	3.22	1.65
RJm6*	M	4.61	1.66	1.30
RHf5*	M	5.92	2.42	1.14
RWh5*	M	6.13	1.48	−1.11
RFc5*	M	6.26	2.97	0.80
RYl6*	M	6.54	2.01	1.10
RQn1*	M	16.93	3.35	0.32
H838	M	17.04	5.69	1.56
RCh1	M	19.27	6.05	0.76
I679	M	21.04	3.78	−0.51
E313	M	21.07	5.92	1.07
RJy	M	21.13	3.16	0.20
X36*	M	21.32	3.35	0.05
CF4*	M	22.98	2.75	−0.81
X39*	M	23.27	3.03	−0.42
RPk*	M	27.53	6.17	−0.05
RI25*	M	27.80	3.30	−4.18

*monkeys studied in Lacreuse et al. (2005)

with three tasks: the delayed non-matching-to-sample (DNMS), assessing visual recognition memory, the spatial condition of the delayed recognition span test (DRST), assessing spatial memory, and the object condition of the DRST, assessing object memory. The tasks consisted of different components that were presented in the following order: the acquisition phase (learning) of the DNMS, the 120 s and the 600 s delays of DNMS, the acquisition phase of the spatial DRST, the spatial DRST and the object DRST. Completion of the entire cognitive battery typically required between 6 and 12 months.

Visual recognition memory (DNMS) The DNMS tests visual recognition memory by requiring the subject to discriminate a novel from a familiar object following a specific delay. *Acquisition:* first, a sample object

was presented over the central location of the test board. The animal was allowed to displace the sample and obtain a reward. The test board was concealed from view. Ten seconds later the recognition trial was begun with the sample object appearing simultaneously with a new object at the left or right side of the test board. In order to obtain the reward, the animal had to recognize the original sample object and choose the novel object. Ten seconds after the monkey's response, a new trial was begun with a new pair of objects. Twenty trials (20 pairs of different objects, "trial-unique" procedure) per day were given until the monkey reached a learning criterion of 90 correct responses in 100 consecutive trials. Objects were randomly drawn from a pool of 1,000 junk objects. The number of trials to reach criterion and the number of errors made to reach criterion were the dependent

variables. *Delays*: after the monkey reached the learning criterion, a delay of 120 s was introduced between the presentation of the sample and the recognition trial. Ten trials a day for 10 days were given (100 trials), followed by 100 trials with a 600 s delay. The percentage of correct responses for each delay was the dependent variable.

Spatial and object memory (DRST) The DRST requires subjects to identify a new stimulus among an increasing set of familiar stimuli. The stimuli were presented serially on a test board consisting of 18 food wells arranged in a 3×6 matrix. In the spatial condition, the stimuli were identical disks presented serially in different locations, and the monkey had to select the disk placed in a new location at each trial. Since all stimuli were identical, except for their location on the board, the task tested spatial memory. In the object condition, the stimuli were different junk objects presented serially at random locations on the board, and the monkey had to select the new object at each trial. The task assessed object memory.

Acquisition phase Prior to formal testing on the spatial-DRST, the monkeys were trained on a simplified version using only a two-disk sequence and the six wells of the middle row of the test board. The monkey was first presented with one disk that could be displaced to obtain a food reward. The screen was lowered for 10 s, during which time the experimenter replaced the disk in its original location and added a new disk in a different location with a reward underneath. The screen was raised, and the monkey had to displace the disk placed in the new location to get the reward. In contrast to the formal testing procedure, no other disk was added; instead, a new trial (with one disk) was begun. Thirty trials per day were given. Learning of the task was achieved when the monkeys produced nine correct responses in ten consecutive trials, three consecutive times. The number of trials and the number of errors made to reach criterion were the dependent variables.

Spatial DRST: the formal testing of the spatial DRST was similar to the acquisition phase, but it used the 18 food wells of the test board and an increasing number of disks. After each correct response (i.e., new location of a disk), an additional disk was added until the monkey made a mistake or until the monkey chose nine correct disks consecutively. Then, a new

trial was begun. Two types of sequences, novel and repeated, were included in the task. For the novel sequences, the order in which the wells were covered by the stimuli was determined by a pseudo-random sequence. Performance on these trials evaluated working memory, since the information was relevant for one trial only. For the repeated sequence, the disks were presented on the tray in a unique sequence that was repeated across trials and across testing sessions, allowing the monkeys to memorize it. Performance on this sequence measured reference memory, since the information provided was relevant across trials. Ten trials were administered each day for a total of 10 days (100 trials, comprising 75 novel and 25 repeated sequences). The mean number of disks that the monkey correctly chose before making a mistake was defined as the spatial memory span (with values between 1 and 8). *Object DRST*: the stimuli were different objects instead of identical disks. At each trial the position of the previously correct stimulus was changed in a random fashion, so that the monkey identified the new stimulus based only on visual, rather than spatial, cues. Two types of sequences, novel and repeated, were included in the task. The novel sequences used new objects at each trial. The repeated sequence used the same set of object across trials that were placed in a predetermined position on the board. The total object memory span (novel + repeated sequences) was the dependent variable for this task.

Fine motor task (Lifesaver task)

Immediately after completing the cognitive battery, monkeys were tested by the Lifesaver test. The Lifesaver test, based on the task described by Zhang et al. (2000), is explained in detail in Lacreuse et al. (2005) and only briefly summarized here. Monkeys had to remove a Lifesaver candy from three metal rods bent into shapes of different complexity (straight, double-S shape and question mark shape), using the left and right hands in alternation. Monkeys were tested twice a week for 8 consecutive weeks, for six trials per session (three shapes × two hands). The dependent variable was the average time required for the monkey to remove the candy from the three shapes across the 48 trials of the study (motor speed). This variable was logarithmically transformed in all analyses.

Analysis

Global cognitive ability was estimated by the cognitive performance index (CPI), a composite summary measure based on individual scores in three cognitive tests, the acquisition of DNMS, the DNMS-120s delay, and the spatial DRST, as described in Herndon et al. (1997). The CPI is a useful index to characterize cognitive impairment in the rhesus monkey (e.g., Sandell and Peters 2003) and to examine the relationships between cognitive performance and other endpoints (e.g., Herndon et al. 1999). In further analyzing the data, we examined whether the CPI and the motor speed differed according to sex and age, using analyses of variances (ANOVAs). Next, to examine whether motor speed in the Lifesaver test could effectively predict global cognitive ability, we used a linear regression, with the CPI as dependent variable and motor speed, age and sex as independent variables. Following this analysis, we examined whether motor speed was related to performance of specific cognitive tasks. This analysis proceeded in two steps. First, we used Pearson's product-moment correlations to explore the relationships among the different cognitive scores and eliminate redundant

variables. Next, we built regression models with motor speed and age as potential predictors of each cognitive score. We used partial regression plots to examine the relationship among variables. These plots display the residuals of the independent variable and the residuals of the dependent variable when both variables are regressed separately on a third variable. All analyses were performed for the whole group and for each sex separately. All analyses were considered significant at $P < 0.05$.

Results

Effects of age and sex on cognitive function and motor speed

The ANOVA on CPI with sex and age as factors indicated that the CPI declined significantly with age ($F(1,26)=9.42$, $P < 0.01$; Figure 1a). As can be seen in Figure 1a, data from three old monkeys were outliers and, in fact, had a CPI approximately 2 SDs below the old group mean. We verified that the effect of age remained significant without inclusion of these three data points in the analysis ($F(1,23)=7.55$, $P < 0.05$).

Figure 1 **a** CPI as a function of age in male (black circles) and female (open circles) rhesus monkeys. The CPI declines significantly with increasing age. **b** Motor speed in the

Lifesaver test as a function of age. Motor speed increased significantly with age in males only

The effect of sex ($F(1,26)=0.015$, ns) and the interaction between sex and age ($F(1,26)=.59$, ns) were not significant. Similar analyses on motor speed indicated that the effects of age ($F(1,26)=2.18$, ns), sex ($F(1,26)=0.99$, ns) and the interaction between sex and age ($F(1,26)=2.78$, $P=0.10$) failed to reach significance. Examination of Figure 1b, however, suggested that motor function may be slower with age in males but not in females. Subsequent one-way ANOVAs revealed, indeed, that age-related motor slowing was significant in males ($F(1,15)=8.55$, $P<0.01$) but not in females ($F(1,11)=0.013$, ns).

Relationships between global cognitive function and motor speed

When the whole group was considered, more than half the variance in CPI ($R^2=0.55$) was predicted by a regression model including motor speed ($t=4.26$, $P<0.001$) and age ($t=-5.28$, $P<0.001$) as independent variables ($F(2,27)=16.77$, $P<0.001$).

Figure 2 shows partial regression plots depicting the relationship between the CPI and age when the effect of motor speed was removed (a) and the relationship between the CPI and motor speed after

the effect of age had been controlled for (b). As can be seen in Figure 2b, at a given age, monkeys with better global cognitive ability obtained worse (slower) motor performance in the Lifesaver test. Further, the relationship was strengthened when only males were considered, with motor speed ($t=3.29$, $P<0.01$) and age ($t=-4.54$, $P<0.001$) predicting as much as 60% of the variance in CPI ($F(2,16)=10.56$, $P<0.01$). In contrast, a similar model in females ($F(2,10)=4.38$, $P<0.05$) showed that age ($t=-2.14$, $P=0.06$) and motor speed ($t=1.97$, $P<0.10$) failed to predict the CPI.

Relationships between individual cognitive scores and motor speed

The next step was to examine which, if any, individual cognitive score(s) was associated with motor speed. In order to eliminate redundant variables and obtain a limited set of dependent variables, we performed Pearson's product moment correlations among the eight cognitive scores (trials and errors to reach criterion in the DNMS, percent correct in DNMS-120s and 600s, trials and errors to reach criterion in the DRST, spatial memory span and object

Figure 2 a,b Partial regression plots in male (black circles) and female (open circles) rhesus monkeys, showing a the relationships between CPI and age, when the effect of motor speed had been controlled for; and b the relationships between CPI and

motor speed after age effects had been controlled for. At a given age, monkeys with better cognitive performance had slower motor skills

memory span). As predicted, this analysis yielded a number of highly correlated variables. For example, the number of trials to reach criterion on the DNMS was positively correlated ($r=0.99$) with the number of errors to reach criterion on the DNMS. Thus, only one of these variables (i.e., number of trials) was retained for subsequent analysis. Proceeding similarly for each dependent variable, we obtained a final set of four variables (number of trials to reach criterion on DNMS, percent correct on DNMS-600s, number of trials to reach criterion on the DRST and spatial memory span) that we submitted to linear regressions with age and motor speed as independent variables.

These analyses revealed that motor speed ($t=-2.72$, $P<0.02$) and age ($t=3.47$, $P<0.01$; $R^2=0.36$; $F(2,25)=7.09$, $P<0.01$) were significant predictors of the number of trials to reach criterion on the DNMS, after removal of two outliers (the oldest male, RI25, and the oldest female, RLt) who had required more than 2,000 trials (i.e., greater than 3 SDs from old group mean) to learn the DNMS (Figure 3). The relationship between motor speed and rate of DNMS learning after age had been controlled for was evident when only males were

considered (motor speed $t=-3.09$, $P<0.01$; age $t=-2.87$, $P<0.02$; $F(2,13)=5.41$, $P<0.02$), but not in females (motor speed $t=-0.22$, ns; age $t=3.0$, $P<0.02$; $F(2,9)=4.41$, $P<0.05$). In females, the only relationship between any cognitive score and motor speed was a non-significant trend for better DNMS-600s performance to be associated with faster motor performance (motor speed $t=-2.19$, $P=0.05$; $F(1,11)=4.82$, $P=0.05$). Motor speed and age were not significant predictors of cognitive performance for any other variable, either in males or in females. It is worth noting that motor speed represented motor performance across repeated testing sessions during which monkeys had learned the task. As expected, motor performance improved from the first (mean=1.25, SEM=0.09) to the last testing session (mean=1.00, SEM=0.08; $t(28)=-2.56$, $P<0.02$). To examine whether learning effects in the motor task affected the results, we redid the analyses with either motor speed at the first session or motor speed at the last session as predictors of cognitive performance. Inclusion of these variables did not significantly alter any of the results.

Figure 3 **a,b** Partial regression plots showing **a** the relationship between the number of trials to reach criterion on the DNMS and age, when the effect of motor speed was removed (two outliers removed), and **b** the relationships between the number of trials to

reach criterion on the DNMS and motor speed, when the effect of age had been controlled for (two outliers removed). Motor speed was associated with slower acquisition of the DNMS after age effects had been controlled for

Discussion

Global cognitive function, as assessed by a summary measure of cognitive functioning, the CPI, declined significantly with age in both sexes, similar to previous results in a larger group of monkeys (Herndon et al. 1997). Age-related slowing of fine motor performance was found only in males, consistent with a previous report on sex differences in age-related motor decline (Lacreuse et al. 2005).

In the present study we focused on the relationship between age-related declines in cognition and age-related slowing of fine motor skills. The CPI, based on scores of three tests, was significantly related to motor speed, when age effects were partialled out. However, contrary to our hypothesis, at a given age, better cognitive scores were associated with *slower* performance in the motor task. The analysis including the individual cognitive scores revealed that motor speed was associated with the rate of acquisition of the DNMS (one of the tasks on which the CPI is based), in such a way that monkeys faster at learning the DNMS were actually slower in the Lifesaver test after age had been controlled for. Interestingly, the association was robust in males but absent in females.

In males both motor speed in the Lifesaver test and DNMS acquisition were impaired with age. However, faster acquisition of the DNMS was related to slower motor performance, when the effect of age was partialled out. These unexpected results suggest that the systems which underlie DNMS learning and fine motor performance may compete under specific learning situations (Poldrack and Packard 2003). Studies in monkeys have shown that lesions of the inferior temporal cortex (Bachevalier and Mishkin 1994), ventral prefrontal cortex (Kowalska et al. 1991) or entorhinal and perirhinal cortices (Zola-Morgan et al. 1989) impair DNMS acquisition. Motor learning, on the other hand, initially involves prefrontal regions of the cortex (Jenkins et al. 1994; Karni et al. 1995), shifting to primary motor cortex, parietal cortex, basal ganglia and cerebellum areas when motor skills become more established (Daselaar et al. 2003; Shadmehr and Holcomb 1997; Toni et al. 1998). Age-related slowing of fine motor function has been attributed to alterations of the nigrostriatal system, including loss of dopaminergic neurons (Emborg et al. 1998; Irwin et al. 1994), reduction of tyrosine hydroxylase and dopaminergic transporter (Gerhardt

et al. 2002; van Dyck et al. 2002), striatal atrophy (Lacreuse et al. 2005; Matochik et al. 2000), and iron accumulation in the striatum (Cass et al. 2006).

The inverse relationship between motor speed and DNMS learning after age had been controlled for may reflect differential recruitment of brain circuits important for cognitive control, and the ability to adapt behavior to current demands and to suppress irrelevant behavior. Cognitive control has been shown to be mediated by fronto-striatal networks (Braver et al. 2002; Casey et al. 2002; Liston et al. 2006) that may provide a dorsal mechanism for the coordination of motor actions and a ventral mechanism for the inhibition of stimulus–response–reward associations (Chudasama and Robbins 2006). The extent to which monkeys recruit these systems may contribute to individual differences in motor performance and DNMS learning: fast motor performance may reflect a deficit in the ability to select appropriate responses in the DNMS, while slow motor function may indicate increased ability to adapt behavior to reward contingencies during DNMS learning. Further testing with tasks directly tapping cognitive flexibility (e.g., card-sort test analogs, reversals, go/no-go tasks) should shed light on the validity of this hypothesis. For example, if motor-efficient monkeys are less able to inhibit responding in tasks of executive function, we might expect an increased number of perseverant responses in monkeys with better motor performance.

The association between motor speed and DNMS learning at a given age was robust in males but absent in females. In females only a non-significant trend was found between faster motor ability and better performance at DNMS-600s. Caution is required in interpreting this result, as a greater number of females would be required to test the validity of the sex difference. At present, we can only speculate that males and females may rely on different neural circuits when performing motor and cognitive tasks. In particular, in light of previous reports on sex differences in the dopaminergic system (Laakso et al. 2002; Mozley et al. 2001; Munro et al. 2006; Pohjalainen et al. 1998), it is plausible that males may be more sensitive to the modulatory effects of dopamine on behavior.

Finally, our results suggest that the ability to predict cognitive performance from motor performance may be limited to certain cognitive tasks. This finding may shed light on the lack of relationship

between sensorimotor performance and cognition usually reported in the rodent literature. Indeed, those studies have almost exclusively used spatial tasks to assess cognitive function. The study by Chen et al. (2004) in Kunming mice is a notable exception. They used an object recognition memory task and an olfactory discrimination task, in addition to a spatial task (radial water maze), to examine the relationships between age-related sensorimotor impairments (beam walking, open field and tightrope) and cognitive decline. Confirming previous findings in rodents (Gage et al. 1989; Gallagher and Burwell 1989; Miyagawa et al. 1998; Rapp et al. 1987), they failed to find an association between sensorimotor performance and spatial task performance. In contrast, sensorimotor impairment was related to performance in the non-spatial tasks (object recognition memory and olfactory discrimination). Since the object recognition task is a hippocampus-dependent cognitive task comparable to the DNMS (Mumby et al. 1996), those findings are directly in line with the present findings in monkeys. Thus, the data of Chen et al. (2004) and our own findings suggest that the relationships between cognition and motor function cannot be adequately described in terms of global measures of cognitive and motor performance, as motor function may only be related to specific non-spatial tasks.

In conclusion, motor speed in the Lifesaver test was related to some aspects of cognition in the rhesus monkey, with slower motor speed predicting faster learning of the DNMS. This relationship was independent of age and more prominent in males than in females. We suggest that this relationship may represent different contributions of the fronto-striatal system to motor control and specific forms of associative learning.

Acknowledgments This work was supported by NIH grants RR00165 and AG00001. We thank Marc Rabner and Katryn Tapper for their assistance with data collection.

References

- Arnsten AF, Goldman-Rakic PS (1985) Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. *Science* 230:1273–1276
- Arnsten AF, Cai JX, Murphy BL et al (1994) Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. *Psychopharmacology* 116:143–151
- Bachevalier J, Mishkin M (1994) Effects of selective neonatal temporal lobe lesions on visual recognition memory in rhesus monkeys. *J Neurosci* 14:2128–2139
- Braver TS, Barch DM, Cohen JD (2002) The role of prefrontal cortex in normal and disordered cognitive control: a cognitive neuroscience perspective. In: Stuss DT, Knight RT (eds) *Principles of frontal lobe function*. Oxford University Press, Oxford
- Camicioli R, Howieson D, Oken B et al (1998) Motor slowing precedes cognitive impairment in the oldest old. *Neurology* 50:1496–1498
- Casey BJ, Tottenham N, Fossella J (2002) Clinical, imaging, lesion, and genetic approaches toward a model of cognitive control. *Dev Psychobiol* 40:237–254
- Cass WA, Grondin R, Andersen AH et al (2006) Iron accumulation in the striatum predicts aging-related decline in motor function in rhesus monkeys. *Neurobiol Aging* (in Press)
- Chen G-H, Wang Y-J, Zhang L-Q et al (2004) Age- and sex-related disturbance in a battery of sensorimotor and cognitive tasks in Kunming mice. *Physiol Behav* 83:531–541
- Chudasama Y, Robbins TW (2006) Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biol Psychol* 73:19–38
- Craik FIM, Salthouse TA (eds) (2000) *The handbook of aging and cognition*. Lawrence Erlbaum Associates, Mahwah, NJ
- Daselaar SM, Rombouts SARB, Veltman DJ et al (2003) Similar network activated by young and old adults during the acquisition of a motor sequence. *Neurobiol Aging* 24:1013–1019
- Emborg ME, Kordower JH (2002) Nigrostriatal function in aged nonhuman primates. In: Erwin JM, Hof, PR (eds) *Aging in nonhuman primates*. Karger, Basel
- Emborg ME, Ma SY, Mufson EJ et al (1998) Age-related declines in nigral neuronal function correlate with motor impairments in rhesus monkeys. *J Comp Neurol* 401:253–265
- Gage FH, Dunnett SB, Bjorklund A (1989) Age-related impairments in spatial memory are independent of those in sensorimotor skills. *Neurobiol Aging* 10:347–352
- Gallagher M, Burwell RD (1989) Relationship of age-related decline across several behavioral domains. *Neurobiol Aging* 10:691–708
- Gallagher M, Rapp PR (1997) The use of animal models to study the effects of aging on cognition. *Annu Rev Psychol* 48:339–370
- Gerhardt GA, Cass WA, Yi A et al (2002) Changes in somatodendritic but not terminal dopamine regulation in aged rhesus monkeys. *J Neurochem* 80:168–177
- Grondin R, Zhang Z, Gerhardt GA et al (2000) Dopaminergic therapy improves upper limb motor performance in aged rhesus monkeys. *Ann Neurol* 48:250–253
- Herndon JG, Lacreux A (2002) The rhesus monkey model as a heuristic resource in cognitive aging research. In: Erwin J, Hof P (eds) *Aging in nonhuman primates*. Karger, Basel
- Herndon JG, Moss MB, Rosene DL et al (1997) Patterns of cognitive decline in aged rhesus monkeys. *Behav Brain Res* 87:25–34
- Herndon JG, Lacreux A, Ladinsky E et al (1999) Age-related decline in DHEAS is not related to cognitive impairment in aged monkeys. *Neuroreport* 10:3507–3511

- Irwin I, DeLanney LE, McNeill T et al (1994) Aging and the nigrostriatal dopamine system: a non-human primate study. *Neurodegeneration* 3:251–255
- Jenkins IH, Brooks DJ, Nixon PD et al (1994) Motor sequence learning: a study with positron emission tomography. *J Neurosci* 14:3775–3790
- Karni A, Meyer G, Jezzard P et al (1995) Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* 377:155–158
- Kluger A, Gianutsos J, Golomb J et al (1997) Patterns of motor impairment in normal aging, mild cognitive decline, and early Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci* 52:P28–39
- Kowalska DM, Bachevalier J, Mishkin M (1991) The role of the inferior prefrontal convexity in performance of delayed nonmatching-to-sample. *Neuropsychologia* 29:583–600
- Krampe RT (2002) Aging, expertise and fine motor movement. *Neurosci Biobehav Rev* 26:769–776
- Laakso A, Vilkmann H, Bergman J et al (2002) Sex differences in striatal presynaptic dopamine synthesis capacity in healthy subjects. *Biol Psychiatry* 52:759–763
- Lacourse A, Diehl MM, Goh MY et al (2005) Sex differences in age-related motor slowing in the rhesus monkey: behavioral and neuroimaging data. *Neurobiol Aging* 26:543–551
- Li KZH, Lindenberger U (2002) Relations between aging sensory/sensorimotor and cognitive functions. *Neurosci Biobehav Rev* 26:777–783
- Li SC, Aggen SH, Nesselroade JR et al (2001) Short-term fluctuations in elderly people's sensorimotor functioning predict text and spatial memory performance: The MacArthur successful aging studies. *Gerontology* 47:100
- Liston C, Watts R, Tottenham N et al (2006) Frontostriatal microstructure modulates efficient recruitment of cognitive control. *Cereb Cortex* 16:553–560
- Matochik JA, Chefer SI, Lane MA et al (2000) Age-related decline in striatal volume in monkeys as measured by magnetic resonance imaging. *Neurobiol Aging* 21:591–598
- Miyagawa H, Hasegawa M, Fukuta T et al (1998) Dissociation of impairment between spatial memory, and motor function and emotional behavior in aged rats. *Behav Brain Res* 91:73–81
- Moore TL, Schettler SP, Killiany RJ et al (2005) Cognitive impairment in aged rhesus monkeys associated with monoamine receptors in the prefrontal cortex. *Behav Brain Res* 160:208–221
- Mozley LH, Gur RC, Mozley PD et al (2001) Striatal dopamine transporters and cognitive functioning in healthy men and women. *Am J Psychiatry* 158:1492–1499
- Mumby DG, Wood ER, Duva CA et al (1996) Ischemia-induced object-recognition deficits in rats are attenuated by hippocampal ablation before or soon after ischemia. *Behav Neurosci* 110:266–281
- Munro CA, McCaul ME, Wong DF et al (2006) Sex differences in striatal dopamine release in healthy adults. *Biol Psychiatry* 59:966–974
- Nieoullon A, Coquerel A (2003) Dopamine: a key regulator to adapt action, emotion, motivation and cognition. *Curr Opin Neurol* 16(2):3–9
- Park D, Schwartz N (eds) (2000) *Cognitive aging: a primer*. Psychology Press, Philadelphia, PA
- Pohjalainen T, Rinne JO, Nagren K et al (1998) Sex differences in the striatal dopamine D2 receptor binding characteristics in vivo. *Am J Psychiatry* 155:768–773
- Poldrack RA, Packard MG (2003) Competition among multiple memory systems: converging evidence from animal and human brain studies. *Neuropsychologia* 41:245–251
- Rapp PR, Rosenberg RA, Gallagher M (1987) An evaluation of spatial information processing in aged rats. *Behav Neurosci* 101:3–12
- Raz N, Williamson A, Gunning-Dixon F et al (2000) Neuroanatomical and cognitive correlates of adult age differences in acquisition of a perceptual-motor skill. *Microsc Res Tech* 51:85–93
- Reeves SJ (2005) A positron emission tomography (PET) investigation of the role of striatal dopamine (D2) receptor availability in spatial cognition. *Neuroimage* 28:216–226
- Reeves S, Bench C, Howard R (2002) Ageing and the nigrostriatal dopaminergic system. *Int J Geriatr Psychiatry* 17:359–370
- Roberts JA (2002) The aged rhesus macaque in neuroscience research: importance of the nonhuman primate model. In: Erwin JM, Hof PR (eds) *Aging in nonhuman primates*. Karger, Basel
- Sandell JH, Peters A (2003) Disrupted myelin and axon loss in the anterior commissure of the aged rhesus monkey. *J Comp Neurol* 466:14–30
- Shadmehr R, Holcomb HH (1997) Neural correlates of motor memory consolidation. *Science* 277:821–825
- Spiriduso WW, MacRae PG (1990) Motor performance and aging. In: Birren JE, Schaie KW (eds) *Handbook of the psychology of aging*. Academic Press, San Diego
- Toni I, Krams M, Turner R et al (1998) The time course of changes during motor sequence learning: a whole-brain fMRI study. *J Neuroimage* 8:50–61
- van Dyck CH, Seibyl JP, Malison RT et al (2002) Age-related decline in dopamine transporters: analysis of striatal subregions, nonlinear effects, and hemispheric asymmetries. *Am J Geriatr Psychiatry* 10:36–43
- Volkow ND, Gur RC, Wang GJ et al (1998) Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. *Am J Psychiatry* 155:344–349
- Voytko ML (1998) Nonhuman primates as models for aging and Alzheimer's disease. *Lab Anim Sci* 48:611–617
- Zhang Z, Andersen A, Smith C et al (2000) Motor slowing and parkinsonian signs in aging rhesus monkeys mirror human aging. *J Gerontol* 55:B473–480
- Zola-Morgan S, Squire LR, Amaral DG et al (1989) Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *J Neurosci* 9:4355–4370