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Executive system dysfunction occurs as early as middle-age in the rhesus monkey

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Abstract

As our understanding of age-related cognitive decline advances, studies are now focusing on identification of those areas of cognitive function that undergo the first changes with age. In the present study, in order to determine whether executive function is sensitive to the aging process, we assessed the performance of 16 monkeys of middle-age (12–19 years of age) on the conceptual set-shifting task, an analogue of the Wisconsin Card Sorting Test (WCST). We compared their performance to that of seven young adult (5–9 years of age) and 18 aged monkeys (20–30). The findings showed that middle-aged monkeys, like those of advanced age, were significantly impaired on the conceptual set-shifting task (CSST). These findings parallel those of recent studies in humans demonstrating an increase in perseverative errors on the WCST by middle-aged as well as aged individuals and, in turn, support the notion that disruption of executive function is one of the earliest changes in cognition to occur in normal aging.

Keywords: Non-human primate; Middle-age; Cognition; Executive Function; Wisconsin Card Sorting Test

1. Introduction

It is well established that normal aging is characterized by a decline in multiple domains of cognitive function including short-term memory, psychomotoric speed, naming, and executive function [1,2,4,37,54]. Of these, executive function (EF) is one of earliest cognitive domains to evidence change in humans [3,25] and non-human primates alike [8,9,41,60,61,76]. Although views on the exact components of EF vary, it is generally agreed that it includes the abilities of set-shifting, planning, working memory, and response suppression (Trans-NIH Executive Function Workshop, January 2003). Among the many tasks that have been developed to assess EF in humans, perhaps the most commonly employed is the Wisconsin Card Sorting Test (WCST [10,31]). This task, which heavily emphasizes set-shifting and response suppression, has been used in studies of normal aging [26], the effects of focal cortical lesions [46,47], head injury [42], attention deficit disorder [40], depression [12], and a host of other neurologic and psychiatric disorders [38]. The popularity of the WCST for use in clinical studies and neuropsychological assessment is due in large measure to its simplicity of design, use of common stimulus classes, amenability to error analyses, and minimum dependence on language. Toward the goal of bringing behavioral studies in humans and animals into parallel, the WCST has been successfully adapted in nearly identical form [49,51,52], or in forms that are analogous to it [24] for use in non-human primates.

With regard to normal aging, the WCST was first used 15 years ago to show that subjects in their 70s and 80s were impaired in executive function [34]. Together with findings from more recent studies [11,32,36,64,65] it is clear that even in earlier stages of aging, there is a diminution in the ability

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to shift and maintain set, as well as an increased tendency to respond to previously correct stimuli (i.e., perseverative errors). We have developed the conceptual set-shifting task (CSST), a direct adaptation of the WCST, as a tool for the study of EF in a rhesus monkey model of normal cognitive aging. In studies using the CSST in aged monkeys, we demonstrated deficits in abstraction, set-shifting and set maintenance in aged rhesus monkeys that parallel those seen in the human studies [49,51]. Specifically, monkeys of advanced age (20–30 years of age, roughly equivalent to humans ages of 60–90 years) were impaired in abstraction and set-shifting on the CSST relative to young adults (5–9 years of age, equivalent to human ages of 15–27 years). Moreover, as found in aged humans, aged monkeys made significantly more perseverative errors during each shift in stimulus set of the CSST [51].

Although these data clearly demonstrate an age-related deficit in executive function, they do not pinpoint the age at which cognitive decline begins. In the present study, we have addressed this important question by using the CSST to determine whether deficits in EF are already evident in monkeys 12–19 years, a range spanning early to late middle-age.

2. Methods

2.1. Subjects

The subjects in this study were 41 rhesus monkeys (*M. mulatta*), weighing between 6.4 and 14.1 kg. Based on an extensive survival study at Yerkes National Primate Research Center [74], which suggests a ratio of 1–3 between monkey and human years of age, we have designated monkeys 5–10 years of age as young monkeys, those 12–19 as middle-aged, and those 20 and older as aged. In this study, the young group consisted of seven animals (5 males and 2 females) from 5 to 9 years of age (Table 1). The data from three of these animals (AM092, AM094, AM095) were included in previous studies as control data [51,52]. The middle-aged group consisted of 16 animals ranging from 12 to 19 years of age (13 males and 3 females). The aged group consisted of 18 animals (11 females and 7 males) ranging from 20 to 30 years of age (Table 1). The data from seven of these animals (AM024, AM048, AM063, AM068, AM090, AM091, AM098) were included in a previous study [52]. One aged male monkey (AM048) did not complete the entire CSST because of a sudden illness. Data from this monkey are only included from conditions completed prior to the onset of illness. All monkeys in this study had known birth dates, complete health records, and were obtained from the Yerkes National Primate Research Center of Emory University. Before entering the study, monkeys received medical examinations that included serum chemistry, hematology, urine analysis, and assessment of visual function. History of splenectomy, thymectomy, exposure to radiation, cancer, organ transplantation, malnutrition, chronic illness including viral or parasitic infections, neurological diseases, or chronic drug administration were explicit exclusion criteria. Once entered into the study, monkeys were individually housed in colony rooms within constant auditory and visual range of other monkeys. A diet of Purina Chow supplemented by fruit was given to the monkeys each day after testing and water was continuously available. Monkeys were maintained under a 12 h light–dark cycle. Monkeys were checked daily by trained observers for health and well-being, and were given a complete medical exam every 6 months.

Following the completion of behavioral testing, each of the monkeys underwent magnetic resonance imaging (MRI) to ensure that none of the monkeys had suffered a major cerebrovascular event, such as a stroke. All of the monkeys in this study had normal MRI findings.

2.2. Behavioral testing

The monkeys in this study were part of a larger study of normal aging and were behaviorally sophisticated, having had experience with the delayed non-matching to sample, delayed recognition span test, and a contrast sensitivity test prior to the administration of the CSST [37,54]. For the present study, an automated pre-training task, a three-choice discrimination task, and the CSST were administered sequentially. Tests were conducted in an automated general testing apparatus that contained a 19 in., touch sensitive, resistive, computer screen, driven by a Macintosh computer. White noise was played on two speakers located within the automated apparatus to mask extraneous sounds. A non-correctional procedure was used throughout testing with M&Ms™ or Skittles™ used as rewards.

An automated pre-training task was used for teaching each monkey to touch the computer screen. This task required the monkey to touch a single stimulus that appeared randomly in one of nine locations on the screen to receive a single piece of M&M™ or Skittles™ candy, the same reinforcement used for all tasks in the study. Pre-training was continued for 20 trials a day until the monkey correctly responded to 20 consecutive trials in a single day. The day after the monkey completed the pre-training task all but three began a simple three-choice discrimination task.

For the discrimination task, and for the subsequent CSST task, the computer screen was divided into a 3×3, unmarked matrix, providing nine distinct locations where a stimulus could be displayed. Monkeys responded by touching one of these locations. The discrimination task was administered to determine if there was a group difference in the ability to discriminate among three stimuli (a pink square, orange cross, and a brown 12-point star) on the basis of the reward contingency. The task presented the monkey with all three stimuli on each trial but their spatial location varied from trial to trial in a pseudo-random order. The pink square was the positive stimulus for all trials and for all monkeys and touching of this stimulus resulted in the delivery of a reinforcement. Touching

Table 1
Sex, age and performance on the three-choice discrimination task for each monkey in the study

Monkey	Sex	Age	Errors on disc task	Non-responses on disc task
Young adults				
AM094[a]	M	5	95	0
AM092[b]	M	6	55	0
AM093	M	6	N/A	N/A
AM095[a]	F	7	97	0
AM128	M	7	68	36
AM132	M	7	65	3
AM163	F	9	210	63
Middle-aged adults				
AM136H	M	12	19	0
AM144X	M	14	9	0
AM113H	M	15	3	0
AM143x	M	15	32	0
AM158H	M	16	16	0
AM190	F	17	12	6
AM037	M	18	18	0
AM101	M	18	37	1
AM216H	M	18	12	23
AM034	M	19	7	0
AM103	M	19	39	19
AM124	M	19	30	0
AM133	M	19	18	0
AM153H	M	19	14	0
AM159	F	19	39	44
AM161	F	19	24	0
Aged adults				
AM123	M	20	7	0
AM126	F	20	18	0
AM160	F	20	0	0
AM177	F	20	250	0
AM162	F	21	30	22
AM178	F	21	2	54
AM179	F	22	209	0
AM090[a]	F	24	62	00
AM164	M	24	2	0
AM189	M	24	49	23
AM068[a]	M	25	10	0
AM063[a]	F	25	38	0
AM098[a]	F	27	38	0
AM107	F	27	9	0
AM024[a]	F	29	18	0
AM048[a]	M	30	N/A	N/A
AM091[a]	M	30	6	0
AM121	M	30	N/A	N/A

N/A: monkey did not complete this task.
[a] Data published in [51].
[b] Data published in [52].

either of the other two stimuli did not deliver a reward, but rather resulted in the darkening of the computer screen for a period of 10 s until the three stimuli were presented again on the next trial. The monkey had to choose the pink square on 10 consecutive trials during one testing session to reach the criterion level of performance. However, a one-way analysis of variance (ANOVA) revealed no significant difference between the performance of monkeys that had the discrimination task and those that had not. This statistical result, along with visual inspection of the data, suggested that experience on the discrimination task did not significantly alter performance on the CSST.

Following the completion of the pre-training and discrimination tasks, formal testing began on the CSST. Each day of testing consisted of 80 trials. During each trial of the CSST, three stimuli were presented in a pseudo-random order appearing in three of nine locations on the computer touch screen (Fig. 1). The stimuli differed in two relevant dimensions, color (red, green, or blue) and shape (triangle, star, and circle). On each trial, three different stimuli were presented

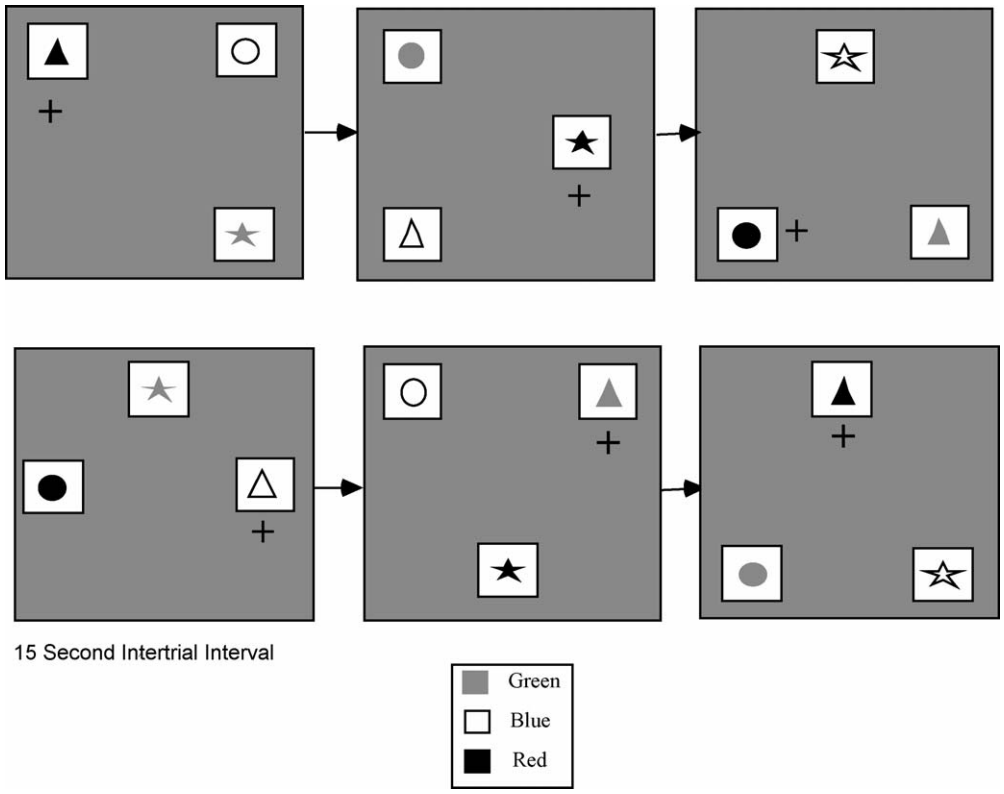

Fig. 1. Schematic of the conceptual set-shifting task (CSST). Each screen (panel) represents one trial. On each trial of the CSST the monkey is presented with three stimuli that vary in shape and color. During the first concept condition, the monkey must choose the red stimulus regardless of its shape as illustrated in the top three screens of this figure. Once the monkey chooses the correct stimulus on 10 consecutive trials, the computer switches the rewarded stimulus on the same testing day, without alerting the monkey. In the second concept condition the monkey must chose the triangle stimulus, regardless of the color as illustrated in the bottom three screens of the figure. Again, when the monkey chooses the correct stimulus for 10 consecutive trials the computer switches the rewarded stimulus on the same testing day, without alerting the monkey. Testing is continued in this same manner for the blue and star concept conditions.

that among them represented all three colors and all three shapes. All nine possible combinations of stimuli (i.e. red triangle, red star, red circle, blue triangle, blue star, etc.) were presented in a pseudo-random but balanced sequence. On each trial, if a monkey did not respond within a one minute time limit, the screen reverted to being blank, a non-response was recorded, and the intertrial interval began. The intertrial interval for each trial was 15 s during which the screen became blank.

Testing consisted of the initial abstraction and acquisition of a conceptual set (red, regardless of shape) and then three additional abstractions and shifts of conceptual set (triangle, blue, and star). The first two abstraction conditions are illustrated in Fig. 1. During the initial abstraction and acquisition of the first conceptual set, the monkey had to choose the red stimulus, regardless of shape, in order to obtain a food reward. Once the monkey chose this stimulus on 10 consecutive trials, the program switched the rewarded contingency during the same testing session, without alerting the monkey. Now, in order to obtain a food reward, the monkey had to choose the triangle, regardless of its color. Again, when the monkey reached a criterion of 10 consecutive responses, the computer switched the rewarded contingency. The blue stimulus then had to be chosen, regardless of its shape, to obtain a food reward. Finally, when criterion was reached on the blue category, the contingency was switched to the last category, star.

2.3. Data analysis

Data collected included the total number of errors, and non-responses to criterion for the discrimination task, the total number errors to criterion for the initial red condition, the total number of errors and perseverative errors for each of the three shift conditions, the total number of perseverative errors and non-responses made across all conditions and the total perseverative errors as a percent of total shift errors (sum total of errors during the shift conditions). A perseverative error was recorded when a monkey made an error by choosing an incorrect stimulus that would have been correct under the previous response contingency. A non-response was recorded when a monkey failed to respond by touching the screen on any trial within one minute of the stimuli appearing on the screen. A non-response was not counted as an error, however it did result in the count of consecutive correct responses toward criterion being reset to zero. Thus, the

total number of trials and errors did not include the number of non-responses.

Separate one-way ANOVAs, with age as the between subjects variable, were run on the number of errors and non-responses on the discrimination task. For the CSST, separate one-way ANOVAs were run on the number of errors on the initial abstraction of the first conceptual set, the total perseverative errors across all shift trials and the number of non-responses across all trials. Separate two-way repeated measures ANOVAs with age as a between subject variable and conceptual set shifts as a within subjects variable were used to compare the performance of the three groups of monkeys in terms of errors and perseverative errors to criterion across each conceptual shift condition. All analyses were followed by Bonferroni post hoc tests when appropriate.

Finally, separate one sample *t*-tests for each age group were used to determine whether the percentage of errors that were perseverative across all three shifts was significantly different from the chance level of making a perseverative error (50%).

3. Results

Prior to running any of the parametric statistics on the data from this study a Cochran test was used to determine whether the data were homogeneous and would allow for analyses with parametric statistics or heterogeneous and violate the principle of homogeneity of variance required for parametric analyses. These Cochran tests all confirmed ($p > 0.05$) that the principle of homogeneity of variance was met.

The total errors and non-responses to criterion on the initial three choice discrimination task are shown in Table 1. Total errors and non-responses were analyzed separately with a one-way ANOVA. These analyses did not show any statistically significant difference between the groups with regards to either errors [$F(2, 34) = 0.566$, $p = 0.573$] or non-responses [$F(2, 34) = 1.16$, $p = 0.3229$] to criterion. This finding confirms that there is no age-related difference with regards to learning a simple visual association or being able to discriminate on the screen the type of stimuli used for the CSST.

In contrast to the spared performance seen on the discrimination task, impairments were seen in the performance of the aged monkeys on the initial abstraction of the CSST. Separate one-way ANOVA revealed a group difference in the number of errors [$F(2, 39) = 5.19$, $p = 0.01$] required to reach criterion on the initial abstraction of the first conceptual set. A Bonferroni post hoc test revealed that the performance of only the aged monkeys differed significantly from that of young adult monkeys ($p \leq 0.009$). As a group, middle-aged monkeys performed as efficiently as young adults on the initial abstraction (Fig. 2). However, a Pearson's *r* correlation revealed a significant linear relationship between age and total errors on the initial abstraction ($r = 0.537$, $p = 0.05$) (Fig. 3).

On the three shift conditions, a two-way repeated measures ANOVA revealed an overall effect of group [$F(2, 38) = 5.08$, $p = 0.01$] and a group by condition interaction [$F(2, 74) = 3.85$, $p = 0.007$] for the total errors across shift conditions. A Bonferroni post hoc test revealed that relative to the young group, both the middle-age group ($p \leq 0.05$) and the aged group ($p \leq 0.05$) were significantly impaired on all three conditions. (Fig. 4). In addition, a Pearson's *r* correlation revealed a significant linear relationship between age and total errors across all three shift conditions ($r = 0.521$, $p < 0.05$) (Fig. 5).

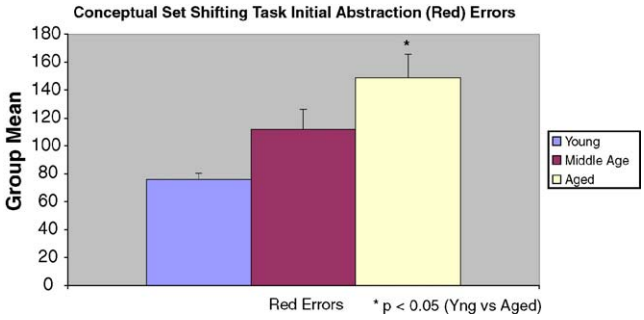

Fig. 2. Group mean errors to criterion (+S.E.M.) for the acquisition of the initial concept condition (red). Asterisk (*) indicates a significant group difference for errors ($p < 0.05$). $n = 7$ for the young group, $n = 16$ for middle-aged group and $n = 18$ for the aged group. Error bars represent standard error.

Total perseverative errors in each shift condition were analyzed with a two-way repeated measures ANOVA. This analysis revealed an overall effect of group [$F(2, 38) = 8.15$, $p = 0.001$] but no significant effect of condition [$F(2,74) = 0.68$, $p = 0.509$] or group by condition interaction [$F(4, 74) = 1.833$, $p = 0.132$]. The significance of group was followed up with a Bonferroni post hoc test that revealed a significant difference between the young and middle-aged animals ($p \leq 0.0019$) and the young and aged animals ($p \leq 0.0006$) (Fig. 6). This was further supported by a Pearson's *r* correlation that revealed a significant linear relationship between age and total perseverative errors ($r = 0.601$, $p < 0.05$) (Fig. 7).

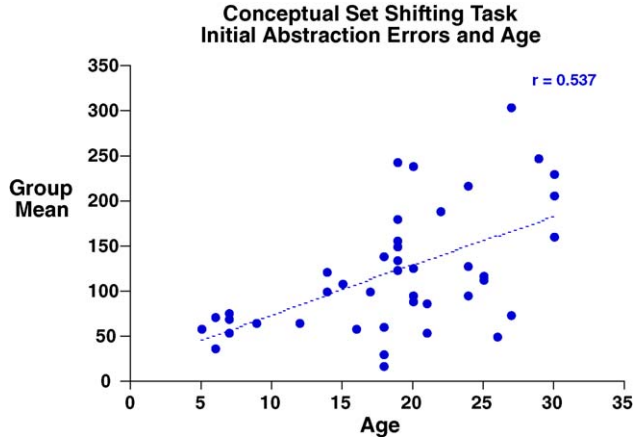

Fig. 3. Scatter plot shows the relationship between total errors to criterion on the initial abstraction and age ($r = 0.537$, $p < 0.05$).

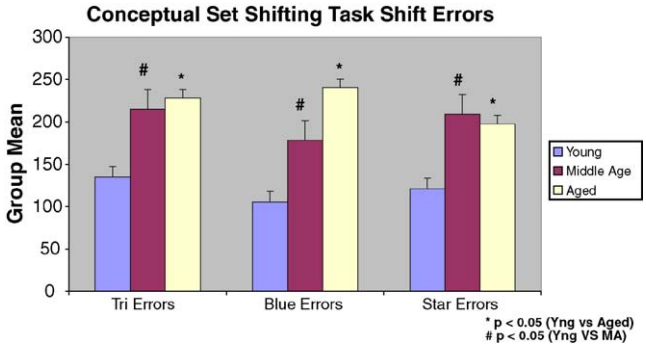

Fig. 4. Group mean errors to criterion (+S.E.M.) for the first (triangle), second (blue) and third (star) shift conditions. Asterisk (*) indicates a significant group difference for errors ($p < 0.05$) between the young and aged animals for all three shift conditions. The number sign (#) indicates a group difference for errors ($p < 0.05$) between the young and middle-aged animals. For the first shift (triangle), $n = 7$ for the young group, $n = 16$ for the middle-aged group and $n = 18$ for the aged group. For the second (blue) and third (star) shifts, $n = 7$ for the young group, $n = 16$ for the middle-aged group and $n = 17$ for the aged group. Error bars represent standard error.

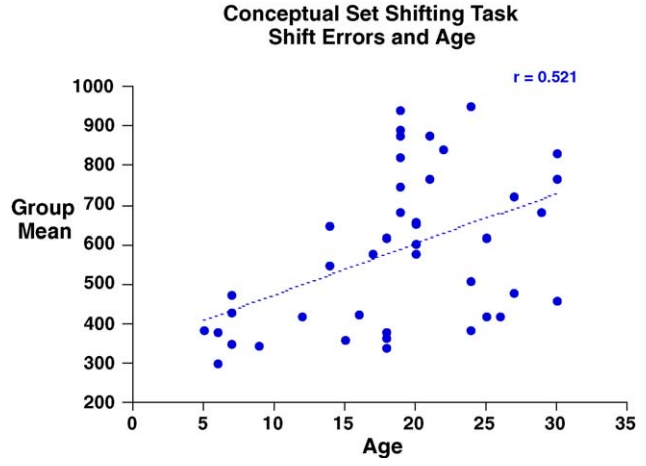

Fig. 5. Scatter plot shows the relationship between total errors to criterion on all three shift conditions and age ($r = 0.521$, $p < 0.05$).

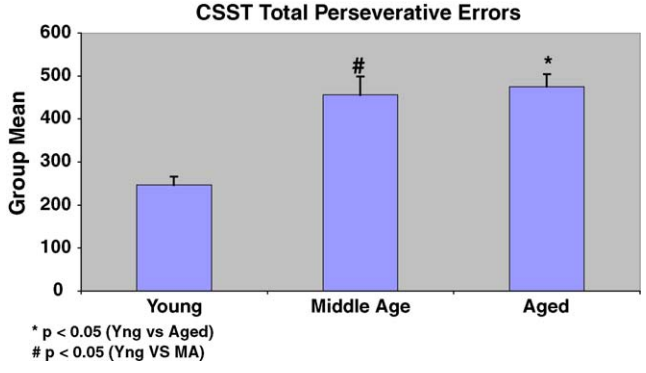

Fig. 6. Group means of total perseverative errors (+S.E.M.) across all three shift conditions. Asterisk (*) indicates a significant group difference ($p < 0.05$) between the young and aged animals and the number sign indicates a group difference ($p < 0.05$) between the young and middle-aged animals. $n = 7$ for the young group, $n = 16$ for the middle-aged group and $n = 17$ for the aged group. Error bars represent standard error.

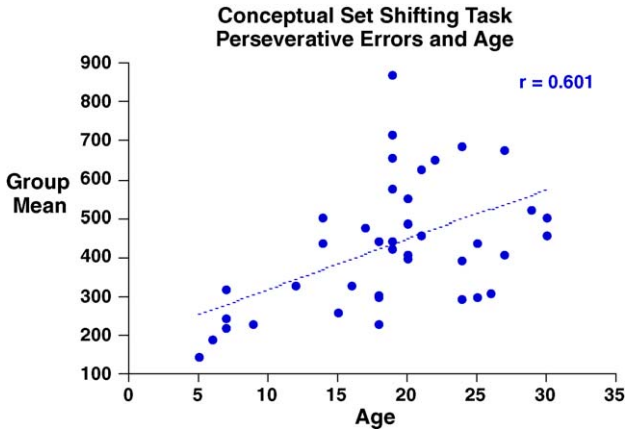

Fig. 7. This scatter plot shows the relationship between total perseverative errors in the shift conditions and age ($r = 0.601$, $p < 0.05$).

As shown in Fig. 6, middle-aged and aged monkeys generally made more perseverative errors than did the younger monkeys. We next employed separate one sample *t*-tests for each age group to determine whether the percentage of errors that were perseverative was significantly different from the chance level of making a perseverative error (50%). These analyses revealed that the middle-aged and aged monkeys made proportionately more perseverative errors than can be accounted for by chance (middle-aged [$t = 2.27$, 15 d.f., $p = 0.04$]; aged [$t = 9.80$, 17 d.f., $p \leq 0.0001$]), while the proportion of perseverative errors made by the young monkeys falls into the range that can be accounted for by chance [$t = 1.98$, 6 d.f., $p = 0.95$]. This confirms that the middle-aged and aged monkeys demonstrated a perseverative response pattern greater than can be accounted for by chance.

There was no significant difference between the groups for the number of non-responses [$F(2, 38) = 0.48$, $p = 0.622$] on the CSST.

4. Discussion

The principal findings of this study are: (1) middle-aged monkeys, like aged monkeys, are impaired in set-shifting, a key component of executive function; (2) both middle-aged and aged monkeys demonstrate a greater tendency toward perseverative responding than do young adult monkeys; (3) impairment in set-shifting shows a strong positive relationship to age; (4) both middle-aged and aged monkeys are unimpaired relative to young adult monkeys on a simple three-choice discrimination task. Together, these results clearly demonstrate that cognitive impairment of executive function begins in middle-age in the rhesus monkey.

4.1. Middle-age and performance on the CSST

Monkeys of middle-age were significantly impaired on the CSST, a test that requires abstraction and shifting of stimulus

set. These findings, together with those from aged monkeys in an earlier study from our laboratory [51] provide strong evidence that at least two components of EF are markedly sensitive to normal aging.

The finding of a marked impairment in set-shifting by monkeys of middle-age was initially of some surprise. To date, few, if any, studies in non-human primates have demonstrated an impairment in any domain of cognitive function in monkeys of middle-age. Yet, of the 16 middle-aged monkeys studied, 9 committed more errors on all shift conditions than the mean number made by young adult monkeys and 5 made errors in the same range as (or near the mean displayed by) monkeys in the older groups. However, the finding is less surprising in the context of recent data showing that, in humans, age-related changes in cognition, executive function in particular, may occur much earlier than previously thought [11,32,36,64,65]. In fact, when one inspects normative data on the WCST in humans, there is the suggestion that not only are individuals of advanced age less efficient on this task, but so are those of middle-age [32]. Indeed, it now appears that EF may be among the earliest domains of cognitive function to exhibit declines with age. Changes begin in the 40 and 50 s, an age range comparable with the middle-aged monkeys in this study [3,32]. In addition, early changes in EF also occur in a variety of neurologic and psychiatric disorders [13,22,23].

A striking aspect of the deficit displayed by middle-aged and aged monkeys was the high frequency of perseverative errors. This deficit appeared to worsen gradually with aging, as indicated by a linear increase in perseverative errors with increasing age. A similar pattern of results was obtained in a recent study examining WCST performance in young, middle-aged and aged humans. In that study, as in our own, there was an increase in perseverative errors on the WCST by both middle-aged and aged individuals and a strong correlation between age and perseverative errors [32].

It is also of interest to note the degree of individual variability in the errors score on the initial abstraction and shift conditions of the CSST for the young, middle-aged and aged monkeys. There is a greater degree of variability among the error scores for the middle-aged and aged animals that parallels human studies demonstrating different rates of cognitive decline with age [1,2]. It is possible that this greater degree of individual variability in the performance by the middle-aged and aged animals represents the difference between successful and unsuccessful aging. If followed longitudinally many of the middle-aged animals with high errors scores on the CSST would likely demonstrate the most striking impairments on this task once they reach advanced age. Future longitudinal studies of cognitive performance on a variety of tests including the CSST would be invaluable in determining the onset of age-related cognitive decline and track the nature of the progression of cognitive decline in aging. The initial steps are currently underway to begin such a study.

The neural substrate of EF has been consistently attributed to the prefrontal cortices and in particular the dorsolateral region (DLPFC). Indeed, lesions of the PFC in both humans and rhesus monkeys does result in deficits on tests of EF. Specifically, performance on the CSST in monkeys with damage to the prefrontal cortex [53], that includes Walker's areas 46 and 9 and small portions of areas 8 and 10, and on the WCST by patients with damage limited to the PFC is characterized by a high incidence of perseverative errors, an inability to shift set once established and an inability to use feedback to modify response patterns [46,47]. The profile of performance closely resembles that reported in this study of middle-aged and aged monkeys on the CSST. Therefore, disruption of the PFC with aging appears to be a potential neurobiological basis for the age-related impairment on the CSST.

4.2. Age-related neurobiological changes in the PFC

Recent magnetic resonance imaging studies have demonstrated that age-related changes in the brain are not uniform across all regions and atrophy is particularly prominent in the frontal lobes [32,63,67,75]. In addition, early and pronounced changes in cerebral blood flow occurs in the frontotemporal regions, which also experience chronic states of reduced cerebral circulation, and decreased oxygen uptake [15,33,71].

Neurobiological studies of area 46 in the dorsolateral prefrontal cortex of young and aged monkeys have been carried out in this animal model [58]. Area 46, located in the wall, roof and floor of the principle sulcus of the DLPFC, is thought to be involved in mediating the cognitive processes of the PFC [43,59]. Extensive neurobiological studies of this region in the rhesus monkey have demonstrated an increase in neuroglial cells with dark cytoplasm, an increase in the amount of inclusion material in the neuroglial cells, and a decrease in the thickness of layer 1 in area 46 of aged monkeys [58]. In addition, there were degenerative changes in the myelin of area 46 and in the underlying white matter in aged monkeys. These changes in myelin correlated with cognitive performance of the monkeys [58]. Recently, we described age-related changes in the microcolumnar organization of ventral area 46 [21] and of action potential firing rates in layer III pyramidal cells of the PFC [18].

Neurochemical studies have revealed decreases in metabolic activity, decreased cortical circulation and depletion of cortical neurotransmitters in the frontal lobe with advancing age [6,14,28,35,44]. Levels of norepinephrine (NE) and dopamine (DA), two monoamine neurotransmitters thought to play a role in the cognitive functions subserved by the PFC, are reduced in aged monkeys and humans alike, with the most significant reductions occurring in the prefrontal and temporal cortices [6,28,30]. Indeed, we have recently reported age-related changes in monoamine receptors in the PFC and found NE was associated with CSST impairments in aged monkeys [50]. This observation is consistent with other studies that show alterations of NE and DA receptors may account in part for age-related changes in cognition [5,7,73].

4.3. Evidence for other cortical areas involved in executive functions

Despite extensive evidence that the prefrontal cortex is involved in mediating cognitive functions such as abstraction and set-shifting and performance on the CSST and WCST, it is likely that other brain structures also contribute. Evidence has implicated the hippocampus, basal ganglia, thalamus and the cingulate gyrus in performance on the WCST [17,19,29,48,56,62,66]. Acting as a network, it has been suggested that the prefrontal cortex, basal ganglia, thalamus and hippocampus may act together, or perhaps act in parallel, for the acquisition of information, attentional set-shifting and planning [16,39,55,70,77].

The hippocampus has been singled out as a structure that may play a role in mediating executive functions [20,27,45]. Patients with medial temporal lobe epilepsy are typically impaired on tests of executive function such as the WCST [57,72]. This has led researchers to suggest that hippocampal dysfunction may alter an individual's performance in tests of executive function. However, while patients with temporal lobe epilepsy are impaired on the WCST, patients with hippocampal sclerosis and anterior temporal lobectomy are not typically impaired on the WCST. It has been suggested that this impairment in patients with temporal lobe epilepsy may be a result of abnormal discharges from this area to other cortical areas, especially the PFC [20,45]. So while changes in the PFC are a plausible explanation of age-related impairments in executive function that we have observed, it will be important to determine the relationship of neurobiological changes in the hippocampus and medial temporal lobe as well.

The cerebellum is another cortical structure that has recently been implicated in executive function [68,69]. Schmahmann [69] has developed a non-human primate model of cerebellar dysfunction. Following bilateral lesions of the dentate nucleus of the cerebellum, monkeys were significantly impaired on abstraction and set-shifting on the CSST. Whether the cerebellum plays an "independent" role in the EF, or is part of a broader neuronal circuit involving the PFC remains to be worked out.

5. Conclusion

Most studies on the neurobiology of cognitive aging have compared young and aged individuals. Very few studies have examined cognitive and neurobiological changes in middle-aged individuals. Because of this, very little is known about the age of onset of cognitive decline. The present study demonstrated that middle-aged monkeys as young as 12 years of age (equivalent to approximately 36 years in humans) already show impairment on the CSST. Middle-age monkeys are impaired on abstraction and set-shifting and demonstrate a greater tendency toward perseverative responding than do young adult monkeys. Further studies of middle-aged individuals are needed to closely examine the nature and timing of the onset of age-related cognitive decline and neurobiological changes in the cerebral cortex. Evidence from this monkey model and a growing body of literature on humans now suggest that deficits in EF may occur earlier in the aging process than previously thought.

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