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Similarities and Differences in Cognitive Deficits and Responsiveness to L-Dopa between Aged and MPTP-Treated Cynomolgus Monkeys Tested on the Same Tasks

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Abstract

Cognitive and motor declines are two major geriatric problems often coexisting in older adults. Also, mild cognitive impairment (MCI) is frequently observed in patients with Parkinson's disease (PD) in addition to motor dysfunction. Amelioration of cognitive deficits, either in patients with PD or in senescence, has proven problematic in the clinic; due, in part, to a poor understanding of the mechanism underlying PD-MCI and age-associated cognitive declines. Thus, a better characterization of similarities and differences between age-associated and disease-related cognitive impairments should help better design therapeutic strategies tailored to restore cognitive functions in either the elderly or PD patients. In the present study, eighteen cynomolgus monkeys were trained and tested on a delayed matching-to-position (DMTP) and delayed matching-to-sample (DMTS) task, including 6 middle-aged, 6 aged, and 6 MPTP-treated animals. After a 3-month break, cognitive testing was resumed in all animals both before and after a 4-day treatment regimen with oral L-dopa. Here, we are reporting that 1) delay-dependent declines in percentage accuracy were seen on both tasks in normal (MPTP naïve) animals while only seen on the DMTP task in MPTP-treated animals, 2) animals with MPTP-induced dopamine deficiency had a greater difficulty learning and performing on the DMTS task compared to normal animals, 3) L-dopa treatment did not improve cognitive performance on either task in any animals, but rather led to a worsening in performance on the DMTP task in normal middle-aged and MPTP-treated animals, and 4) cognitive declines correlated with age only on the DMTS but not on the DMPT task. Our results suggest that cognitive impairments seen in animals with MPTP-induced dopamine deficiency differ from those seen in aged animals.

Keywords: Aging; Parkinsonian; Cognition; MPTP; L-dopa

Introduction

Human aging is a universal phenomenon. From a healthcare perspective, a major concern with an aging population is a higher prevalence of two major geriatric problems: cognitive and motor decline, both of which often coexist in older adults [1]. For example, gait impairment and number of falls is more prevalent in individuals with dementia than in those with normal aging; also the severity of the gait disability is directly related to cognitive impairments [2]. In addition, recent evidence suggests that mild cognitive impairment (MCI) is frequently observed in patients with Parkinson's disease (PD) [3] and often involves impairments in executive function, attention, visuospatial performance, and working memory [4,5]. Moreover, studies suggest that cognitive impairments is one of the most common and important non-motor aspects of PD, which greatly affects function and quality of life [5,6]. Nevertheless, only roughly 25% of patients with dementia are recognized by clinicians in routine clinical care [7]. Therefore, many key questions about treatment, care, and diagnosis remain unanswered [5]. As a result, although a few effective treatments for the motor symptoms of PD are currently available, amelioration of the cognitive deficits in patients with PD has proven problematic in the clinic due, at least in part, to a poor understanding of the mechanism underlying PD-MCI [5]. Thus, a better characterization of the similarities and differences between age-associated and disease-related motor and cognitive impairments should help basic and clinical investigators to develop novel strategies and methods to better diagnose and slow the progression of both PD-MCI and MCI to dementia [8,9].

The progressive impairment of motor abilities seen in aging includes bradykinesia, stooped posture and shuffling gait, all of which resemble the clinical features of PD [10,11]. It has been hypothesized that the similarities in movement dysfunction in aging and PD may

arise in part from alterations of the same neuronal circuitry, namely the nigrostriatal dopamine pathway [12]. Functional changes of the nigrostriatal dopaminergic system have been demonstrated in both PD and aging. In PD, it is characterized by an extensive, >60% loss of midbrain dopaminergic neurons in the substantia nigra pars compacta (SNc) and >80% loss in dopamine content in the striatum [13]. In older adults, there is evidence for a widespread decline of dopaminergic neuromodulation in cortical as well as subcortical regions such as the basal ganglia [14,15]. Other studies also demonstrated that the number of dopaminergic neurons in the SNc decreases by 7% per decade in humans [16]. However, major changes in dopaminergic neurons (i.e. >50% loss) do not occur during normal aging in either human or animal models of aging; suggesting that dopamine cell loss alone cannot account for age-related motor deficits [17-19]. However, there are other significant changes occurring in the nigrostriatal dopaminergic pathway during aging such as decreases of dopamine receptors, functional alterations in dopamine release and uptake/ changes in dopamine transporter (DAT) markers [20,21]. Along these lines, motor and cognitive impairments can not only be studied in

animal models of aging but can also be reproduced in monkeys dosed with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [22,23]. Although the nonhuman primate model of PD does have its limitations (i.e., other pathological features of PD such as Lewy body formation are not produced [24], it remains one of the most relied upon models for testing PD therapies [25]. The PD model reliably produces a stable lesion of striatal DA neurons, with concomitant motor deficits observed in PD. Like PD patients, monkeys given MPTP respond to typical anti-parkinsonism drugs and exhibit the same motor complications that result from their long-term [26-29]. The results from these published studies suggest that animals with MPTP-induced motor and cognitive deficits could be used to screen new therapeutic agents for tackling both motor and cognitive dysfunctions seen in patients with PD-MCI.

Methods and Materials

Animals

Eighteen (8 male and 10 female) research naïve cynomolgus monkeys (*Macaca fascicularis*) weighting from 4.7 to 7.2 kg were used for this study. Six were normal middle-aged animals (8-12 years old), six were normal aged animals (17-19 years old) and six were dopamine deficient animals (8-12 years old) induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP was administered 12-15 months prior to conducting the present behavioral study and consisted of a unilateral administration of MPTP via the left carotid artery (average dose of 0.52 ± 0.02 mg/kg) using previously described procedures [26,28]. This was followed by an additional dose administered 3 months later by intravenous injection (average dose of 0.3 mg/kg) to produce a bilateral but one sided dominant parkinsonian model [30]. During the study, animals were individually housed in stainless steel cages at the primate facility of Wincon Theracells Biotechnologies Co, LTD. in Nanning, Guangxi China, which is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. All animals were maintained on a 12-h light/12-h dark cycle with water available *ad libitum*. Toys, a mirror and food supplements were routinely provided to promote psychological well being for all tested animals. The ethical issues for using nonhuman primates and procedures involved in the study were thoroughly reviewed and approved by the Animal Care and Use Committee, in accordance with the Association for Reassessment and Accreditation of Laboratory Animal Care guideline. Procedures and the timeline for each group used in the study are summarized in Table 1.

Motor assessment

Motor functions were assessed in all animals from video records using a standardized rating scale that was patterned after the human Unified Parkinson's Disease Rating Scale [27,28,31,32]. In addition, an acute L-dopa challenge (L-dopa/carbidopa 10:1, 250 mg by oral gavage) was conducted in MPTP-treated animals one month before cognitive testing began. Behavioral responses to the acute L-dopa challenge were recorded for later analysis. All video records used in the study were labeled with only the animal ID number (a six-digit code) and the study name, and then were sent to the University of Kentucky for final evaluations. A neuroscientist who is experienced in both primate models and human patients blindly assessed the video records for changes in motor function. Each feature of motor dysfunction was scored from 0 (normal) to 3 (severe disability) points in the following categories: bradykinesia, rigidity, tremor, posture and balance instabilities [27,31,32].

Cognitive assessment

All animals went through a 2-3 week basic training period during which time they were acclimated to a primate chair later used for oral L-dopa administration under fully conscious, alert conditions. Prior to training for cognitive testing, the animals were also acclimated to the cognitive testing panels in the testing-cage environment.

As shown in Figure 1, two test panels were custom-designed for cognitive testing in the testing-cage. These panels were modeled after both the WGTA [33] and our previously described automated movement assessment panel used to test motor learning, working memory and upper limb motor function in rhesus monkeys [34]. The panel used for the delayed matching-to-position (DMTP) task (Figure 1A) has two identical opaque sliding screen doors (one on each side) that are used to blind the animals for a specified delay. The testing tray has two built-in food wells that are perpendicularly attached to the main panel and are covered with two identical opaque Lexan sliding access doors. The DMTP task is designed as a spatial working memory and/or color discriminating task. The panel used for the delayed matching-to-sample (DMTS) task (Figure 1B) has three arm portals in the mainframe panel and three food wells, rather than two as for the DMTP panel. As shown in Figure 1B (lower panel), various objects were randomly attached on sliding doors and used as cues during each test session. In addition, a sliding door with an identical object, as the cue, was used to cover one of lateral food wells during a test. Based on published procedures and preliminary studies, three variable delays ranging from 0-10sec were used for both tasks [35-37].

Before the collection of any baseline data, animals were trained for 4-5 weeks to learn how to perform each cognitive task. The daily training sessions for each animal were less than 30 minutes to minimize fatigue and boredom. The training started with the DMTP panel, which was attached to the doorway of the testing-cage with both screen doors opened allowing the animals to view the target stimulus for 3-5 seconds. Next, the two identical screen doors and the sliding doors covering two food wells were closed for a specified delay. The food item was randomly distributed between the left and right wells and delays were also randomly selected during the daily training sessions. Behavioral readiness for the DMTP panel was concluded when each animal completed 30 trials with a success rate of 95% or better without any delay. The animals were then trained to operate the DMTS Panel, which was also attached to the doorway of the testing-cage similar to the DMTP panel. The training started with allowing the animal to open the middle sliding door on which there was an object (cue) attached that permitted the animals to retrieve a food item from the food well. Once the animals were regularly pushing the middle sliding door away and taking treats from the middle food well, they were then trained to operate the left or right food wells. Both food wells were covered with the sliding doors, with one door bearing a novel object and the other door the cue object. The trial was considered a success, when the animal chose the correct well. The readiness for the DMTS panel was concluded when each animal completed 30 trials with a success rate of 70% for MPTP-treated or better for normal animals without any delay (Figure 2).

There were 10 trials for each delay and 30 trials for each daily testing session. Three months after the baseline data collection, all animals were treated with L-dopa/carbidopa 10:1 with a dose of 125 mg b.i.d for 4 days. The cognitive testing for DMTP and DMTS tasks without delay was then resumed 12 hours after the last oral dose of L-dopa. No cognitive testing was conducted during the 3-month holiday period.

MPTP treatments	Training	Baseline cognitive testing	3-month break from cognitive testing	Oral L-dopa treatment	Post L-dopa Cognitive testing
MPTP: ICA+IV 24 months recovery and behavioral evaluations (n=6)	Normal middle aged (n=6), MPTP-treated (n=6) and aged (n=6) animals enter the study	One lab tech performed DMTP and one performed DMTS task	No cognitive testing Motor assessments (n=18)	L-dopa/ cabidopa 125 mg b.i.d by oral gavage for 4 days (n=18)	Both DMTP and DMTS task were performed on all animals 20 hour after the last dose of L-dopa (n=18)
	1) chair-training for oral L-dopa administration; 2) panel training for cognitive testing (n=18)	Monkeys and tasks were randomly selected for each testing session	Acute L-dopa challenge in MPTP-treated animals (n=6)		

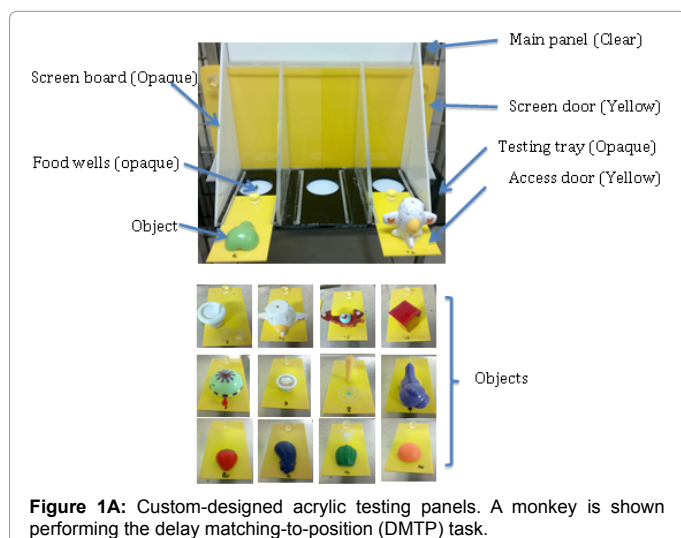**Table 1:** Experimental design and timeline.

Figure 1A: Custom-designed acrylic testing panels. A monkey is shown performing the delay matching-to-position (DMTP) task.
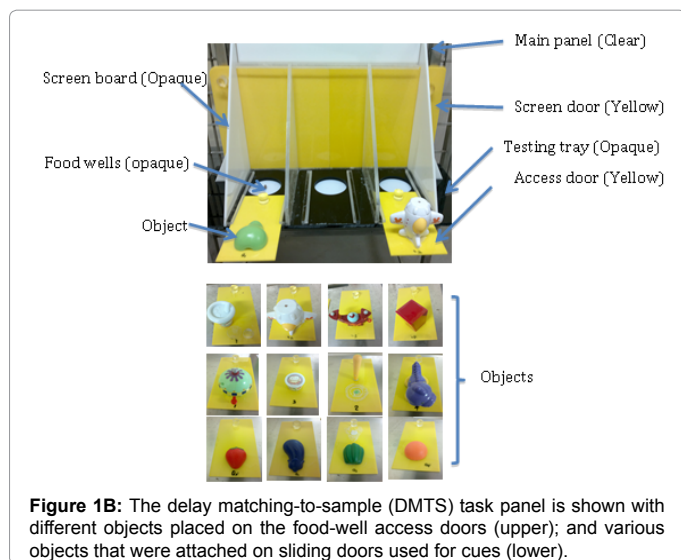

Figure 1B: The delay matching-to-sample (DMTS) task panel is shown with different objects placed on the food-well access doors (upper); and various objects that were attached on sliding doors used for cues (lower).

Statistics

All data are presented as mean ± SEM. Paired *t*-tests (two-tailed) were used to analyze L-dopa-induced improvements of motor function in MPTP-induced parkinsonian monkeys. Differences in cognitive performance between experimental groups (normal middle-aged, middle-aged with MPTP treatment and normal aged) as well as learning curve effect were evaluated by a one-factor analysis of variance (ANOVA) followed by Bonferroni's multiple comparison tests. The relationships between age and cognitive tasks were subsequently analyzed by pairwise Pearson correlations. A value of $p<0.05$ was considered significant in all analyses. All statistical analyses were conducted using Prism 6 GraphPad Software (San Diego, CA).

Results

Motor assessment

The most active animals during the video recording period were the normal middle-aged monkeys. Overall, the aged animals were less active and expressed mild rigidity of the limbs and a stooped posture compared to their younger counterparts. In contrast, more notable motor dysfunction was seen in the six MPTP-treated animals; including bradykinesia, stooped posture and balance instability as well as upper and lower limb rigidity, especially on the contralateral side to the intracarotid MPTP administration (Figure 3A open circle). Despite those parkinsonian features, MPTP-treated monkeys could use both hands for walking, climbing, retrieving and manipulating food. Consistent with previous studies [26,28], action tremors were observed in some animals, but was not a major feature in these MPTP-lesioned monkeys as indicated in Figure 3A (open circle). Furthermore, all MPTP-treated animals positively responded to L-dopa as supported by a significant 39% improvement in the total motor dysfunction score recorded after acute L-dopa administration (Figure 3B). L-dopa-induced improvements were observed primarily for bradykinesia and rigidity of both upper and lower limbs (Figure 3A close circle).
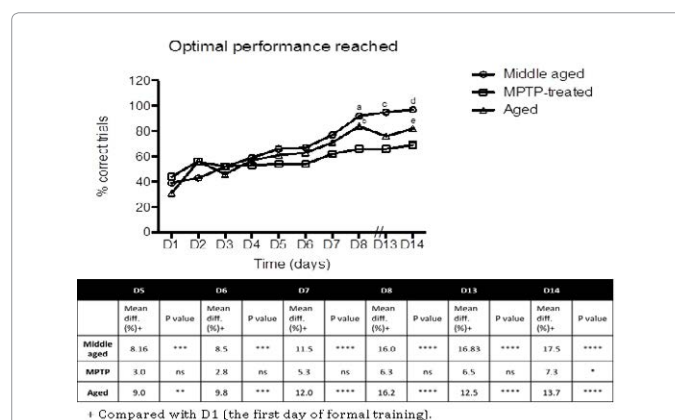

Figure 2: DMTS task learning curve. A gradual daily improvement was observed over time in middle-aged and aged animals. By contrast, smaller improvements were seen in MPTP-lesioned parkinsonian monkeys (lower panel). Significant differences were found on the 8th day of training between MPTP-treated versus middle-aged animals (P<0.01) and MPTP-treated versus aged animals (P<0.05); similar significances were also seen on the last day of training.

Cognitive assessment

All animals were successfully trained to perform on both testing panels and readily enjoyed the food items selected for cognitive testing, supporting that motivation did not appear to be a confounding variable. All animals learned to use the DMTP task panel without difficulty, as shown by a 100% accuracy performance level achieved in normal middle-aged and aged animals, and a 95% accuracy performance level in MPTP-treated animals without delay by the end of the 8th day of training. A significant difference in performance on the DMTS task was found on the 8th day between MPTP naïve groups and MPTP-treated animals and remained statistically significant up to the last day of training (Table in Figure 2). By contrast, the DMTS panel appeared more challenging than the DMTP panel particularly for the MPTP-treated animals. At the end of the 14th day of training, the percentage of correct trials on the DMTS panel failed to reach 100% in the middle-aged animals (as seen on DMTP task), and only reached about 87% in the aged animals and about 70% in the MPTP-treated animals (Figure 2). The data collected during training for the DMTS task also indicated that the average performance of the normal, MPTP naïve animals including aged animals was significantly improved daily, while improvements in MPTP-treated monkeys were less incremental as seen in the normal animals. A significant difference was only found on the last day of training when compared the data collected on the first day of training (Table in Figure 2).

In subsequent testing sessions on the DMTP task, a delay-dependent decline in percentage accuracy was observed in all animals. The percentage of correct trials was reduced with a 3 sec delay from 100% to 93% (P<0.01) in middle-aged animals (Figure 4A left side columns) and from 97% to 70% (P<0.01) in MPTP-treated animals (Figure 4B, left side columns). By contrast, the decline with 3s delays in aged animals only showed a trend down (P>0.05 but <0.1) (Figure 4C, left columns). As shown in Figure 4A-C (left side columns), the performance worsened as the delay was increased up to 10 sec. In fact, the percentage of correct trials was further decreased to 84% in middle-aged animals (Figure 4A left side columns), to 73% in aged animals (Figure 4C left side columns) and even to 53% in MPTP-treated monkeys (Figure 4B left side columns). The comparison between the three groups indicated significant differences between MPTP-treated animals and both normal middle-aged and aged animals at the 3 sec delay, as well as between MPTP-treated animals and normal middle-aged animals at the 10 sec delay (Figure 5, left panels).

A delay-dependent reduction of percentage accuracy was also found on the DMTS task but was somewhat different when compared to that seen on the DMPT task. As indicated in Figure 4A-C (right side columns), the percentage of correct trials on the DMTS panel was reduced from 87% to 71% with a 3 sec delay and further decreased to 58% with a 10 sec delay in aged monkeys (Figure 4C right side columns). Although a 13% reduction was found with 3 and 10 sec delays in the middle-aged animals, no significant differences were seen between 3 and 10 sec delays (Figure 4A right side columns). By contrast, there were virtually no changes in MPTP-lesioned animals between 0, 3 and 10 sec delays (Figure 4B right side columns). Statistically, no significant differences were detected between 3 and 10 sec delays in both middle-aged and MPTP-treated animals (Figure 4A and B right side columns). Intergroup comparison revealed that highly significant differences were found between parkinsonian and MPTP naïve animals with 0 and 3 sec delay; between middle aged and MPTP-treated; between middle aged and aged animals (Figure 5, right panels). A strong age-related decline in percentage of correct trials ($r^2=0.67$, P=0.0006) was also

found among the normal animals on the DMTS panel but not on the DMTP panel ($r^2=0.001$, P=0.82) (Figure 6).

The cognitive testing that took place 3 months after the initial testing phase but before the 4-day L-dopa treatment regimen suggested that all animals still remembered how to perform the tasks. This is supported by a >95% accuracy found on the DMTP task and similar percentages of correct trials were seen on the DMTS task when compared to the initial testing phase (Figure 7A open bars). The data collected after the 4-day L-dopa challenge indicated that no improvement was observed for both tasks (Figure 7A and B). On the contrary, although virtually no changes were seen in the aged animals, reductions in percentage correct trials were observed on the DMTP task in both middle-aged and MPTP-treated animal (Figure 7A).

Discussion

Results from the present study highlight similarities and differences between normal macaques and macaques with MPTP-induced dopamine deficiency in performing different cognitive tasks. Our findings indicate that, 1) delay-dependent declines in percentage accuracy were seen on both tasks in middle aged and aged animals while only seen on the DMTP task in MPTP-treated animals, 2) monkeys with MPTP-induced dopamine deficiency, modeling human PD, were poor learners on the DMTS task compared to aged animals, 3) L-dopa administration did not improve cognitive function, but rather led to a worsening in performance on the DMTP task in normal middle-aged and MPTP-treated animals, but not in aged animals, and 4) cognitive declines correlated with age only on the DMTS but not on the DMPT task.

Our observations are in accordance with those of an earlier study in which a group of macaques was chronically treated with low doses of MPTP, and then shown to exhibit cognitive deficits using the delayed matching-to-sample, object retrieval, and discrimination reversal tests [38]. Attention and executive function deficits were also reported in this chronic low dose MPTP model of PD [24]. Taken together, the results from the current study and previously published data demonstrate the
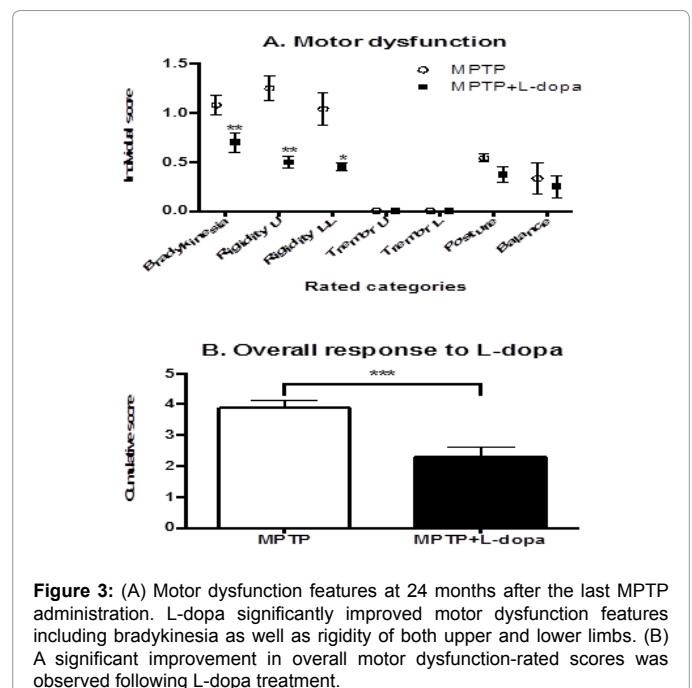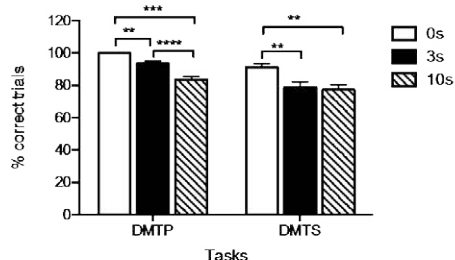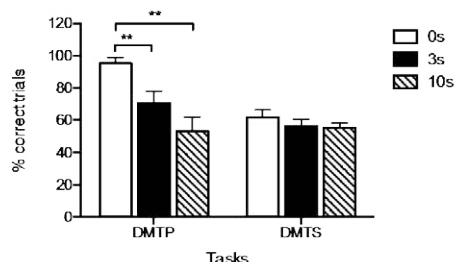

Figure 3: (A) Motor dysfunction features at 24 months after the last MPTP administration. L-dopa significantly improved motor dysfunction features including bradykinesia as well as rigidity of both upper and lower limbs. (B) A significant improvement in overall motor dysfunction-rated scores was observed following L-dopa treatment.
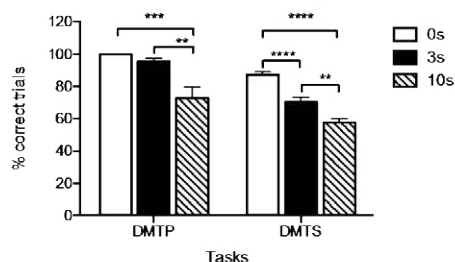
Figure 4: Percentage of correct trials for each delay-matching task: DMTP task (left side columns) and DMTS task (right side columns). Delay-dependent changes were recorded in normal middle-aged (A), MPTP-treated (B) and normal aged monkeys (C). Profound changes at the longer delays were seen in aged animals on both tasks, whereas smaller changes were seen in middle-aged animals. No significant changes were found in MPTP-treated animals on the DMTS task although comparable changes seen in aged were observed in DMTP task. The error bars indicate the mean±SEM. ****P<0.0001, **P<0.01.

might weaken the link between reward and action and dampen the transmission of dopaminergic signals to cortical areas that control goal-directed behavior [12]. However, the result from the present study did not support the notion that only increasing dopamine content in the nigrostriatal system by oral L-dopa administration can improve cognitive function. There is the consensus that the integrities of the dopamine, serotonin, and acetylcholine systems decline during the course of usual aging and those neurotransmitter systems broadly innervate various neural circuitries throughout the brain to modulate key aspects of cognition; such as attention and memory as well as reward-mediated motivational influences on behavior control [43-47] In addition, clinical studies performed in healthy elderly humans have reported poor or no benefit from dopamine replacement therapy (L-dopa) on age-related motor decline either [48].

The mechanism underlying MPTP-induced cognitive deficits are poorly understood. It has been reported that loss of asymmetric spine synapses occurs in the prefrontal cortex of MPTP-treated animals that are motor asymptomatic but cognitively impaired [49]. Since these asymmetric spine synapses on dendrites in the prefrontal cortex are dopamine-dependent, cognitive deficits exhibited in parkinsonian animals could be due to a reduction of dopamine neurotransmission in that brain region. However, results from a recent study do not support this hypothesis. Schneider and colleagues (2013) reported that L-dopa improved motor deficits but could further disrupt cognition in MPTP-
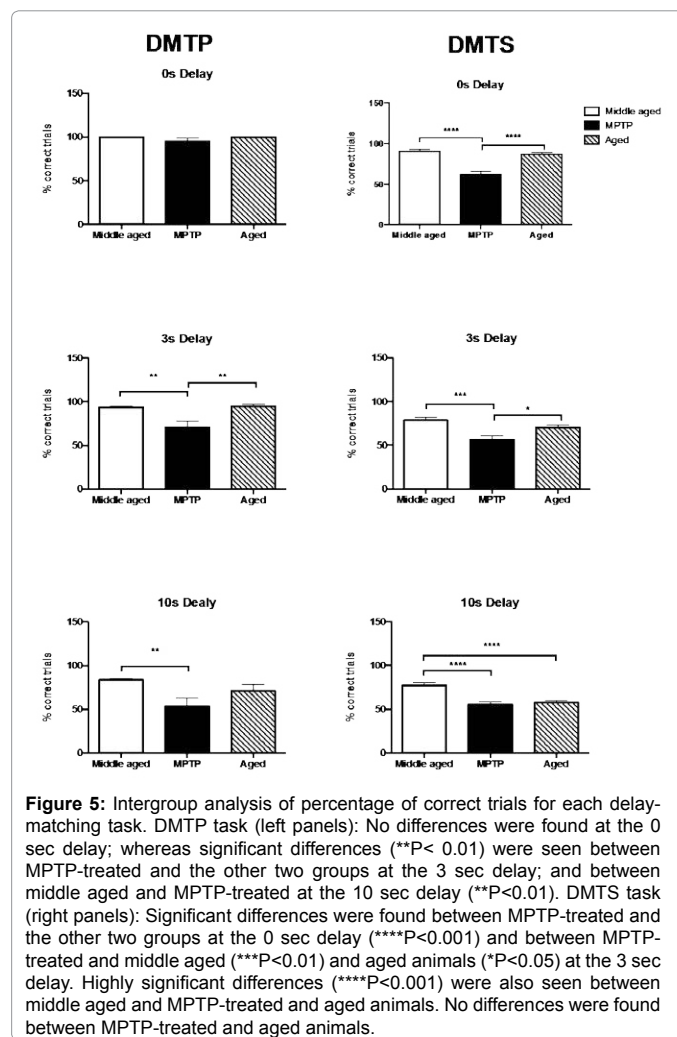

Figure 5: Intergroup analysis of percentage of correct trials for each delay-matching task. DMTP task (left panels): No differences were found at the 0 sec delay; whereas significant differences (**P< 0.01) were seen between MPTP-treated and the other two groups at the 3 sec delay; and between middle aged and MPTP-treated at the 10 sec delay (**P<0.01). DMTS task (right panels): Significant differences were found between MPTP-treated and the other two groups at the 0 sec delay (****P<0.001) and between MPTP-treated and middle aged (***P<0.01) and aged animals (*P<0.05) at the 3 sec delay. Highly significant differences (****P<0.001) were also seen between middle aged and MPTP-treated and aged animals. No differences were found between MPTP-treated and aged animals.

ability to produce a non-human primate model that recapitulates both motor and non-motor aspects of human PD, which could be used to advance our understanding of physiopathological alterations in the nigrostriatal system and/or other brain systems [5].

In the present study, the performance on both cognitive tasks worsened along with increasing delays more so in aged versus younger animals suggesting that longer delays may present a greater mnemonic burden on aged animals than their younger counterparts. Results from previous studies suggest that proficiency by macaques on the DMTS task depends upon unimpaired hippocampal and inferotemporal cortical function [39,40], whereas acquisition of the "matching" component of the task is dependent upon frontotemporal cortical interactions [41,42]. Current findings point to an age-related decline of pre- and postsynaptic marker of the DA system in several brain regions relevant to reward-based learning and decision-making. The reduction of dopaminergic neurons may lead to weaker phasic responses of the midbrain to motivationally salient events in the elderly. The decrease of DAT and dopamine receptors in the striatum
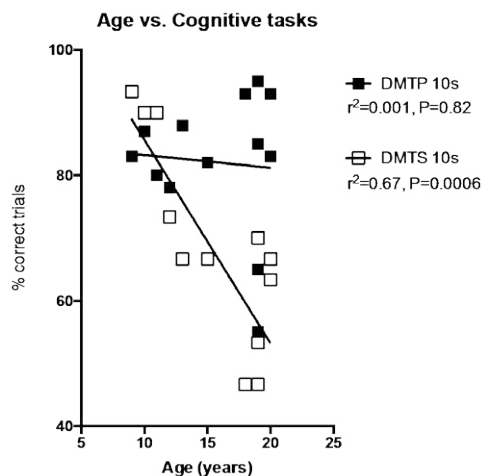
Figure 6: Correlations between age and DMTP or DMTS tasks. The relationships between age and the two different cognitive tasks were analyzed by Pearson correlation. A strong correlation was found between age and DMTS but not DMTP task. Pearson's correlation value and linear fit are shown.
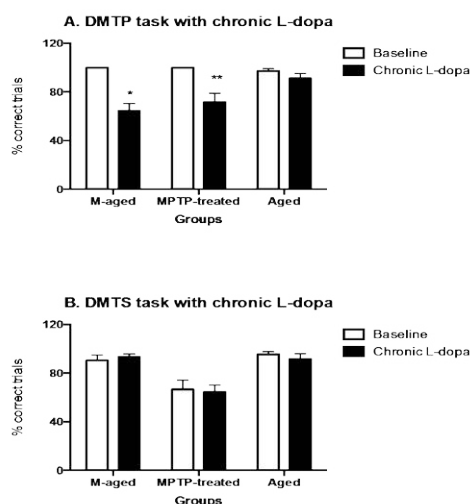

Figure 7: Responsiveness to a 4-day L-dopa administration. No improvements in percentage of correct trials were found for either the DMTP (A) or the DMTS (B) task in any of the three experimental groups. In contrast, a reduction in percentage accuracy on the DMTP (A) task was seen in normal middle-aged and MPTP-treated animals. No delay was employed.

treated monkey. They hypothesized that dopamine replacement therapy may provide a therapeutic amount of dopamine to more heavily denervated basal ganglia areas and improved certain deficits primarily related to basal ganglia-based motor dysfunction; but may also cause a dopamine overload to other areas, such as the frontal cortex, resulting in impairment of cognitive functions associated with these regions [50]. The result from the present study appeared in agreement with this previously published report. In addition, a recent study revealed that cortical glutamate levels decrease in monkeys with MPTP-induced dopamine deficiency (Fan et al., 2014). Glutamate is the principle excitatory neurotransmitter in the CNS, which plays a critical role in cognitive functions. It has been documented that changes in AMPA receptors number and/or function are a core feature of synaptic plasticity and age-related cognitive decline [51]. In addition, degeneration of cholinergic projection fiber from the basal

forebrain is possibly another reason of cognitive impairment in PD [4]. Taken together, these data suggest that the mechanism(s) underlying cognitive impairment in MPTP-treated animals and in patients with PD goes beyond dysfunction of the dopamine system only [52,53].

Studies showed that PD patients with severe cognitive impairment, such as executive defects in planning, initiation, monitoring of goal-directed behavior and working-memory deficits can be attributed to dysfunction in the frontal-striatal basal ganglia circuits; whereas visuospatial and memory deficits, which are more representative of posterior cortical functioning, are exhibited in patients with milder cognitive impairment. This data suggests that the functional decline of fronto-striatal connections is relatively slower than that seen with posterior-cortical connections [4,54]. The data from the present study indicates that key differences exist between MPTP-naïve and MPTP-treated animals, particularly the difference between aged and MPTP-treated animals on the DMTS task as shown in Figure 6. These findings provide further insights that different brain circuitries, cortical regions and neurotransmitter systems may underlie cognitive deficits seen in aging and in PD [4,48,55]. The results from the current study also suggest that MPTP-treated animals were much slower in learning how to perform the DMTS task than aged animals. Although the exact underlying mechanism has not been fully explored, it has been generally accepted that the role of the basal ganglia (primarily the dorsal and ventral striatum) and the dopaminergic inputs play a role on learning to predict/obtain rewards. In particular, the basal ganglia are necessary for non-motor, incremental learning of stimulus-response association [56]. The findings from this nonhuman primate study appears in agreement with published clinical studies in which PD patients were impaired at incremental learning of the task, but had intact explicit memory [57,58]. Interestingly, compared with MPTP-lesioned animals, older monkeys exhibited a better learning capability on the DMTS task, which is in line with earlier human studies [59,60].

In the present study, all aged animals demonstrated the ability to learn short-term memory related task such as the DMTS test, although they were less proficient at the longer delay compared with younger animals. The outcome from the current study may suggest that older cynomolgus monkeys could learn new skills. However, one must exercise caution in interpreting the data because the age of the normal animals used in this study ranged from 8-19 years old, which is roughly equivalent to 27-57 years old in human age and may not be representative of a larger population. A different conclusion may be reached if more animals with a broader range of ages were used. Nevertheless, results from human studies revealed that cognitive plasticity and preserved ability to learn and adapt new information into their behavior can be seen in patients with MCI [61]; and that improvements in cognition can be achieved by using carefully designed restorative and compensatory strategies [62-66].

In conclusion, results from the present study complement and further extend previous reports on age-associated and MPTP-induced cognitive impairments in non-human primates. Our results suggest that cognitive impairments seen in animals with MPTP-induced dopamine deficiency differ from those seen in aged animals. Overall, our data supports that different brain regions and circuitries may contribute to cognitive impairments seen with MPTP-induced dopamine deficiency versus those seen in normal aging. Thus, therapeutic treatments may need to be tailored to address these differences to restore cognitive functions in the elderly or in patients with PD.

Conflict of Interest

The authors have no conflict of interests.

Acknowledgements

References

1. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM (2012) Gait and cognition: a complementary approach to understanding brain function and the risk of falling. J Am Geriatr Soc 60: 2127-2136.

2. Tinetti ME, Speechley M, Ginter SF (1988) Risk factors for falls among elderly persons living in the community. N Engl J Med 319: 1701-1707.

3. Aarsland D, Marsh L, Schrag A (2009) Neuropsychiatric symptoms in Parkinson's disease. Mov Disord 24: 2175-2186.

4. Pagonabarraga J, Kulisevsky J (2012) Cognitive impairment and dementia in Parkinson's disease. Neurobiol Dis 46: 590-596.

5. Svenningsson P, Westman E, Ballard C, Aarsland D (2012) Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol 11: 697-707.

6. Rektorova I (2011) Mild cognitive impairment exists in Parkinson's disease. J Neural Transm 118: 1179-1183.

7. Hu M, Cooper J, Beamish R, Jones E, Butterworth R, et al. (2011) How well do we recognise non-motor symptoms in a British Parkinson's disease population? J Neurol 258: 1513-1517.

8. Simon SS, Yokomizo JE, Bottino CM (2012) Cognitive intervention in amnestic Mild Cognitive Impairment: a systematic review. Neurosci Biobehav Rev 36: 1163-1178.

9. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, et al. (1996) Prevalence of parkinsonian signs and associated mortality in a community population of older people. N Engl J Med 334: 71-76.

10. Smith CD, Umberger GH, Manning EL, Slevin JT, Wekstein DR, et al. (1999) Critical decline in fine motor hand movements in human aging. Neurology 53: 1458-1461.

11. Cass WA, Grondin R, Andersen AH, Zhang Z, Hardy PA, et al. (2007) Iron accumulation in the striatum predicts aging-related decline in motor function in rhesus monkeys. Neurobiol Aging 28: 258-271.

12. Hämmerer D, Eppinger B (2012) Dopaminergic and prefrontal contributions to reward-based learning and outcome monitoring during child development and aging. Dev Psychol 48: 862-874.

13. Fearnley JM, Lees AJ (1991) Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114 : 2283-2301.

14. Backman L, Lindenberger U, Li SC, Nyberg L (2010) Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. Neurosci Biobehav Rev 34: 670-677.

15. Bannon MJ, Whitty CJ (1997) Age-related and regional differences in dopamine transporter mRNA expression in human midbrain. Neurology 48: 969-977.

16. Reeves S, Bench C, Howard R (2002) Ageing and the nigrostriatal dopaminergic system. Int J Geriatr Psychiatry 17: 359-370.

17. Irwin I, DeLanney LE, McNeill T, Chan P, Forno LS, et al. (1994) Aging and the nigrostriatal dopamine system: a non-human primate study. Neurodegeneration 3: 251-265.

18. Emborg ME, Ma SY, Mufson EJ, Levey AI, Taylor MD, et al. (1998) Age-related declines in nigral neuronal function correlate with motor impairments in rhesus monkeys. J Comp Neurol 401: 253-265.

19. Gerhardt GA, Cass WA, Yi A, Zhang Z, Gash DM (2002) Changes in somatodendritic but not terminal dopamine regulation in aged rhesus monkeys. J Neurochem 80: 168-177.

20. Bannon MJ, Poosch MS, Xia Y, Goebel DJ, Cassin B, et al. (1992) Dopamine transporter mRNA content in human substantia nigra decreases precipitously with age. Proc Natl Acad Sci U S A 89: 7095-7099.

21. Gerhardt GA, Cass WA, Henson M, Zhang Z, Ovadia A, et al. (1995) Age-related changes in potassium-evoked overflow of dopamine in the striatum of the rhesus monkey. Neurobiol Aging 16: 939-946.

22. Schneider JS, Kovelowski CJ 2nd (1990) Chronic exposure to low doses of MPTP. I. Cognitive deficits in motor asymptomatic monkeys. Brain Res 519: 122-128.

23. Decamp E, Schneider JS (2004) Attention and executive function deficits in chronic low-dose MPTP-treated non-human primates. Eur J Neurosci 20: 1371-1378.

24. Capitanio JP, Emborg ME (2008) Contributions of non-human primates to neuroscience research. Lancet 371: 1126-1135.

25. Gash DM, Zhang Z, Ovadia A, Cass WA, Yi A, et al. (1996) Functional recovery in parkinsonian monkeys treated with GDNF. Nature 380: 252-255.

26. Bankiewicz KS, Oldfield EH, Chiueh CC, Doppman JL, Jacobowitz DM, et al. (1986) Hemiparkinsonism in monkeys after unilateral internal carotid artery infusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Life Sci 39: 7-16.

27. Ovadia A, Zhang Z, Gash DM (1995) Increased susceptibility to MPTP toxicity in middle-aged rhesus monkeys. Neurobiol Aging 16: 931-937.

28. Ding F, Luan L, Ai Y, Walton A, Gerhardt GA, et al. (2008) Development of a stable, early stage unilateral model of Parkinson's disease in middle-aged rhesus monkeys. Exp Neurol 212: 431-439.

29. Clarke CE, Sambrook MA, Mitchell IJ, Crossman AR (1987) Levodopa-induced dyskinesia and response fluctuations in primates rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). J Neurol Sci 78: 273-280.

30. Oiwa Y, Eberling JL, Nagy D, Pivirotto P, Emborg DM, et al. (2003) Overlesioned hemiparkinsonian non human primate model: correlation between clinical, neurochemical and histochemical changes. Front Biosci 8: 155-166.

31. Kurlan R, Kim MH, Gash DM (1991) Oral levodopa dose-response study in MPTP-induced hemiparkinsonian monkeys: assessment with a new rating scale for monkey parkinsonism. Mov Disord 6: 111-118.

32. Smith RD, Zhang Z, Kurlan R, McDermott M, Gash DM (1993) Developing a stable bilateral model of parkinsonism in rhesus monkeys. Neuroscience 52: 7-16.

33. Harlow HF, Settlage PH (1948) Effect of extirpation of frontal areas upon learning performance of monkeys. Res Publ Assoc Res Nerv Ment Dis 27 (1 vol.

34. Gash DM, Zhang Z, Umberger G, Mahood K, Smith M, et al. (1999) An automated movement assessment panel for upper limb motor functions in rhesus monkeys and humans. J Neurosci Methods 89: 111-117.

35. Arnsten AF, Cai JX, Murphy BL, Goldman-Rakic PS (1994) Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. Psychopharmacology (Berl) 116: 143-151.

36. Arnsten AF, Cai JX, Steere JC, Goldman-Rakic PS (1995) Dopamine D2 receptor mechanisms contribute to age-related cognitive decline: the effects of quinpirole on memory and motor performance in monkeys. J Neurosci 15: 3429-3439.

37. Cai JX, Arnsten AF (1997) Dose-dependent effects of the dopamine D1 receptor agonists A77636 or SKF81297 on spatial working memory in aged monkeys. J Pharmacol Exp Ther 283: 183-189.

38. Schneider JS, Roeltgen DP (1993) Delayed matching-to-sample, object retrieval, and discrimination reversal deficits in chronic low dose MPTP-treated monkeys. Brain Res 615: 351-354.

39. Jackson WJ (1984) Regional hippocampal lesions alter matching by monkeys: an anorexiant effect. Physiol Behav 32: 593-601.

40. Sahgal A, Iversen SD (1978) Categorization and retrieval after selective inferotemporal lesions in monkeys. Brain Res 146: 341-350.

41. Bussey TJ, Wise SP, Murray EA (2002) Interaction of ventral and orbital prefrontal cortex with inferotemporal cortex in conditional visuomotor learning. Behav Neurosci 116: 703-715.

42. Stern CE, Sherman SJ, Kirchhoff BA, Hasselmo ME (2001) Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. Hippocampus 11: 337-346.

43. Cools R, Roberts AC, Robbins TW (2008) Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci 12: 31-40.

44. Noudoost B, Moore T (2011) The role of neuromodulators in selective attention. Trends Cogn Sci 15: 585-591.

45. Shohamy D, Adcock RA (2010) Dopamine and adaptive memory. Trends Cogn Sci 14: 464-472.

46. Volkow ND, Wang GJ, Baler RD (2011) Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci 15: 37-46.

47. Li SC (2012) Neuromodulation of behavioral and cognitive development across the life span. Dev Psychol 48: 810-814.

48. Darbin O (2012) The aging striatal dopamine function. Parkinsonism Relat Disord 18: 426-432.

49. Elsworth JD, Leranth C, Redmond DE Jr, Roth RH (2013) Loss of asymmetric spine synapses in prefrontal cortex of motor-asymptomatic, dopamine-depleted, cognitively impaired MPTP-treated monkeys. Int J Neuropsychopharmacol 16: 905-912.

50. Schneider JS, Pioli EY, Jianzhong Y, Li Q, Bezard E (2013) Levodopa improves motor deficits but can further disrupt cognition in a macaque Parkinson model. Mov Disord 28: 663-667.

51. Henley JM, Wilkinson KA (2013) AMPA receptor trafficking and the mechanisms underlying synaptic plasticity and cognitive aging. Dialogues Clin Neurosci 15: 11-27.

52. Kehagia AA, Barker RA, Robbins TW (2010) Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol 9: 1200-1213.

53. Klein JC, Eggers C, Kalbe E, Weisenbach S, Hohmann C, et al. (2010) Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. Neurology 74: 885-892.

54. Owen AM (1997) Cognitive planning in humans: neuropsychological, neuroanatomical and neuropharmacological perspectives. Prog Neurobiol 53: 431-450.

55. Morrison JH, Baxter MG (2012) The ageing cortical synapse: hallmarks and implications for cognitive decline. Nat Rev Neurosci 13: 240-250.

56. Foerde K, Shohamy D (2011) The role of the basal ganglia in learning and memory: insight from Parkinson's disease. Neurobiol Learn Mem 96: 624-636.

57. Knowlton BJ, Squire LR, Gluck MA (1994) Probabilistic classification learning in amnesia. Learn Mem 1: 106-120.

58. Knowlton BJ, Mangels JA, Squire LR (1996) A neostriatal habit learning system in humans. Science 273: 1399-1402.

59. Calero MD, Navarro E (2004) Relationship between plasticity, mild cognitive impairment and cognitive decline. Arch Clin Neuropsychol 19: 653-660.

60. Fernández-Ballesteros R, Zamarrón MD, Tàrraga L (2005) Learning potential: a new method for assessing cognitive impairment. Int Psychogeriatr 17: 119-128.

61. Valenzuela M, Sachdev P (2009) Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. Am J Geriatr Psychiatry 17: 179-187.

62. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, et al. (2002) Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA 288: 2271-2281.

63. Oswald PA (1996) The effects of cognitive and affective perspective taking on empathic concern and altruistic helping. J Soc Psychol 136: 613-623.

64. Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, et al. (2006) Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA 296: 2805-2814.

65. Fan XT, Zhao F, Ai Y, Andersen A,Hardy P et al. (2014) Cortical glutamate levels decrease in a non-human primate model of dopamine deficiency. Brain Res 1552: 34-40.

66. Grondin R, Zhang Z, Yi A, Cass WA, Maswood N, et al. (2002) Chronic, controlled GDNF infusion promotes structural and functional recovery in advanced parkinsonian monkeys. Brain 125: 2191-2201.