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Published online: xx xx, xxxx

IMR Press

Original Research

Development of a novel gripping test for the evaluation of the finger fine motor ability in MPTP-treated monkeys

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DOI:10.31083/j.

Assessing the finger fine motor ability is extremely important. However, conventional behavioral tests in monkeys are complicated and costly. We attempted to develop a new task to assess the precise finger grip in Parkinson's disease monkeys based on the principles of objectification, multipurpose, and simplification. This study involved seven adult male cynomolgus monkeys. A gripping test based on the previous food reaching test was developed. Parallel experiments of food reaching test and gripping test affected by the treatments of levodopa and deep brain stimulation of the subthalamic nucleus were performed to verify the utility of the gripping test. We found that gross motor ability (measured by food reaching test) could be significantly improved by both the subthalamic nucleus and levodopa administration, which reproduced the results of our previous study. The finger fine motor ability (measured by the gripping test) could be significantly improved by levodopa administration, but not by the subthalamic nucleus. Our results verified the utility and reliability of the gripping test, which is a simple, convenient, and objective task for evaluating the finger fine motor skill in Parkinson's disease monkeys. Mechanisms of the efficacy of deep brain stimulation on fine motor ability require further investigation.

Keywords

Parkinson's disease; levodopa; deep brain stimulation; behavioral test; finger fine motor skill; gross motor skill

1. Introduction

Gross motor skills and fine motor skills are two important types associated with motor ability (Brandwayn et al., 2019). Gross motor skill is the movement ability of the arms, legs, and entire body. In contrast, fine motor skill is the movement ability of hands, lips, tongue, and especially the fingers and thumb. Fine motor skill is important for activities of daily living because most occupational tasks use fine motor skill, such as operation, writing, and playing the piano. The fine motor skill is also affected in Parkinson's disease (PD) patients. Symptoms such as micrographia, the first symptom of the fine motor skill in PD patients, which occurs in 63% of PD patients (Wagle Shukla et al., 2012), or shaky pentagon drawing are not rare in PD patients. It has been reported that dysfunction of precision grip is also common in PD state and is an important cause in the reduction of activities of daily living in PD patients (Gorniak et al., 2013). Thus, investigation of the fine motor skill in PD state has been increasingly attended to by clinicians.

In humans, the finger fine motor skill is the most important for activities of daily living, which involves the precision grip between the thumb and index finger (Asakawa et al., 2016b). Several behavioral tests were developed to evaluate the dysfunction of the precision grip, such as conventional Purdue pegboard test (Tiffin and Asher, 1948), box and block task (BBT) (Mathiowetz et al., 1985), and grip force tasks (Neely et al., 2013). However, assessments of the fine motor skill in PD animals are difficult to achieve. To our knowledge, the monkey is the only animal that can mimic the finger fine motor, mainly the precision grip of humans. However, the available assessments for measuring the finger fine motor are incredibly complicated. As early as Gash et al. (1999) developed a movement assessment panel to measure the finger fine motor in the monkey. The researcher had to train the monkey to obtain the food through a moving panel in front of the home cage. Data on hand movements were recorded and then submitted to a computer to process. The method requires complicated equipment, motor analysis software, and experienced experimenter, making it expensive and time-consuming. Therefore, a more straightforward, cheaper, and more convenient tool to measure the finger fine motor ability in monkeys is expected.

We previously appealed the principles of objectification, multipurpose, and simplification (OMS) during the development of the behavioral test in PD subjects (Asakawa et al., 2016a,b, 2019). We have developed a food reaching test (FRT) that is convenient, simple, and objective to assess the gross motor skill surrounding the elbow in PD monkeys (Asakawa et al., 2012); however, this method can only measure the gross motor skill. Nishimura et al.

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(2007) introduced a method to measure the precision grip motor in monkeys with spinal injury (Nishimura et al., 2007), but this was not developed for PD model and inappropriate to directly use in PD monkeys. Based on these previous works, we attempted to develop a simple task as per the principle of OMS, namely, to achieve assessment of gross motor ability and precision grip motor ability simultaneously in monkeys (multipurpose).

In this study, as the first step to develop the multipurpose task, we developed a novel but simple method to measure the precision grip motor ability using the same system of FRT in monkeys, namely, gripping test (GT). Using monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), we verified the performance and utility of GT in PD monkeys by observing the efficacy of treatments with levodopa (L-dopa) and deep brain stimulation of the subthalamic nucleus (STN-DBS). In the future, we will combine GT with FRT to make a comprehensive hand reaching test. We believe that these behavioral tests will be useful to measure the finger fine motor ability in PD monkeys.

2. Materials and methods

2.1 Animals

Seven adult male cynomolgus monkeys (*Macaca fascicularis*) (aged 7-8 years with a bodyweight of 5-6 kg) (Asakawa et al., 2012) were used in this study. Monkeys were raised in an air-conditioned room (temperature, 25 ± 1 °C; humidity, 55 ± 5%; on a 12-h light/dark cycle). Food was provided twice per day (10: 00 am and 5: 00 pm). Water was freely available. Monkeys were randomly divided into two groups using a simple coin toss method: three (MPTP-treated monkeys) were treated with 0.3 mg/kg MPTP hydrochloride (Sigma-Aldrich Co., MO, USA) intravenously administrated for 30 days with three-day interval until PD symptoms presented as our previous study (Asakawa et al., 2012) and four were intact controls.

All monkeys were treated as per the Guidelines for the Care and Use of Laboratory Animals of the National Institute of Health. All experiments were approved by the Animal Care and Use Committee of Hamamatsu University School of Medicine (permission number 2011051).

2.2 Surgical processes

Under anesthesia with intramuscular ketamine (10 mg/kg) followed by intravenous propofol (10 mg/kg/h), a unilateral stimulating electrode was stereotactically implanted in STN of MPTP-treated monkeys guided by an extracellular recording system described in our previous study (Asakawa et al., 2012). In brief, we used an indirect method described by Pouratian et al. (2011) to target the dorsolateral (motor) region of the STN (Houshmand et al., 2014) associated with the anterior commissure (AC) and posterior commissure (PC). T1-weighted magnetic resonance imaging (MRI) images of monkeys were used to determine the preliminary 3D coordinates, where we implanted a recording electrode. According to Saleem's atlas, the location of the target is approximately at the 6 mm posterior the AC line, and 5.0 mm lateral of the midline (Saleem and Logothetis, 2012). The 3D coordinates of STN were conformed until we recorded the characteristic extracellular electrical activity of STN. The final 3D coordinates of the dorsolateral region of STN in MPTP-treated monkeys were as follows: AP, + 14.5 mm; LP (left), 5.9 mm; and depth, 29.8 mm in monkey 1; AP, + 13.2 mm; LP (left), 4.9 mm; and depth, 29.0 mm in monkey 2; and AP, + 14.9 mm; LP (left), 5.5 mm; and depth, 30.0 mm in monkey 3. The location of the tip of the electrode was confirmed to have targeted the STN by the extracellular electrical activity recorded during the operation. We used the same deep brain stimulation (DBS) parameters as the previous study: frequency, 145 Hz; wave width, 60 μs; and the lowest current intensity to stop tremor as the stimulating current (1.0 v, 1.4 v, and 2.8 v in monkeys 1, 2, and 3, respectively) (Asakawa et al., 2012).

2.3 Behavioral assessments

2.3.1 Food reaching test

FRT was used to evaluate the gross motor ability of the elbow. Because the efficacy of DBS and L-dopa treatments had been verified in our previous study, in this study, FRT was employed to confirm the symptoms of monkeys and the stability of the experimental system. The previous study described in detail the procedures of FRT (Asakawa et al., 2012). Briefly, the monkey was seated in a handmade wooden box with a transparent glass board underlying a hole in the face board. There was an adjustable horizontal platform in front of the hole where cubical potatoes were placed (1 × 1 × 1 cm). Five potatoes with a distance of 5 cm were arranged in a line perpendicular to the glass surface. The monkeys were trained to take the food one by one with the released hand through the hole. The break-off time was set at 180 s. The time from when the monkey's hand first appeared at the hole to the time when the monkey's hand disappeared from the hole with the fifth potato was recorded and defined as the time required for FRT completion (FRT time). The interval between each measurement was set at 5 min, ensuring that the monkey finished eating all potatoes in the mouth.

2.3.2 Gripping test

We developed a novel GT to measure the fine finger motor ability in monkeys (Fig. 1). We used the same handmade wood box (length, 60 cm; width, 70 cm; height, 150 cm) for the GT. The same as FRT, we set a transparent glass board (width, 26 cm; height, 16 cm) underlying a hole (diameter, 6 cm) in the face board and made two holes (diameter, 6 cm) in the sideboard to fix two high-speed video cameras. The distance of the three holes from the ground was 80 cm, and that of the two-side hole from the face board was 5 cm. The monkey was set at the same location of FRT. Namely, the monkey was placed in the center of the glass, the distance from the monkey's mouth to the frontal glass was 10 cm, and the height from the monkey's eyes to the platform was 15 cm. A transparent organic glass tube with a narrow vertical groove (length, 3 cm; width, 1 cm) was stretched into the front hole horizontally to give food to the monkey. The distance from the tip of the tube to the front hole was 5 cm, which was the same as the video camera. The food piece (cubical potatoes, 0.5 × 0.5 × 0.5 cm) was supplied from a smaller plastic pod with a nail in the head through the tube.

The monkeys were deprived of 1/2 food from the previous day of the task. On the day of the task, monkeys were deprived of all food. The monkeys were trained to reach for the cubical potato through the narrow groove and to grasp it with the index finger and thumb. Because the time of gripping is short, it cannot be measured by eyes using a stopwatch. Therefore, we recorded the entire

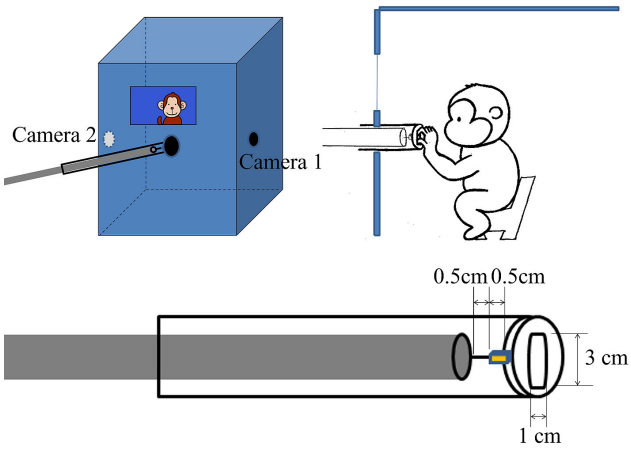

Figure 1. The sketch of the gripping test (GT).

gripping procedure using two high-speed video cameras (Panasonic, GS320, Japan). We set the recording speed of the video cameras at 30 frames/s, that is, 1 frame will take 0.033 s. The "gripping motor" was defined as the time from when the monkey's fingers appeared in the tube and got the food to when the fingers disappeared from the tube. By counting the video frames during one gripping motor, we can measure the time needed for the monkey to finish the precise gripping, which was defined and calculated as the index of "gripping time" (frames $\times$ 0.033 s) (Fig. 5). The break-off time was set at 10 s.

2.4 Confirmation of the utility of GT

Fig. 2 presents the experimental design of this study. All experiments were performed on three consecutive days. FRT was used to evaluate the gross motor of the elbow, whereas the novel GT was adopted for measuring the finger fine motor ability in animals. We performed GT and FRT on the first experimental day after L-dopa administration (with DBS off). Performing GT after L-dopa administration aimed to verify the usability of GT. If GT is useful, it should be able to present the "full recovery" of PD symptoms, which were verified by our previous study (Asakawa et al., 2012). The dose of L-dopa (Sigma, 30 min after benderizine [Sigma]; 10: 1 ratio) was 50 mg/kg, as decided by the previous study (Asakawa et al., 2012). We selected such a hefty dose of L-dopa to achieve a full recovery and keep medical efficacy before the entire tasks were finished (140 min after injection). GT was performed after 10 FRTs, with a 40-min interval. The same procedures were performed in two healthy monkeys on the second experimental day when all of the MPTP-treated monkeys were kept at rest to wash out the effects of L-dopa. FRT and GT were performed on the third experimental day in MPTP-treated monkeys, first during DBS off state. To confirm the stability of the DBS system, we performed FRT before and after GT (defined as FRT a and FRT b, respectively) in the condition that DBS was on. Each task interval was set at 40 min, based on our experience, when monkeys were allowed to get a full rest.

2.5 Statistical analysis

SPSS software (v19.00, IBM, IL, USA) was used for all statistical analyses. Data normality was tested using the Shapiro-Wilk test. All data were recorded as mean $\pm$ standard deviation and were acquired and analyzed by three independent experiments. A two-way analysis of variance (ANOVA) followed by Bonferroni post hoc correction was used to perform multiple comparisons. $P < 0.05$ was considered as statistical difference.

3. Results

3.1 Confirmation of the experimental system

Fig. 3 presents the results of FRT before (FRT a) and after GT (FRT b). No significant change was found between FRT a and FRT b when DBS was on in MPTP-treated monkeys, both in DBS ($F = 0.217$, $P = 0.643$, $df = 359$) and non-DBS sides ($F = 0.210$, $P = 0.886$, $df = 359$) (Fig. 3). We, therefore, confirmed the stability of the experimental system.

The results of the FRT affected by treatments of DBS and L-dopa are presented in Fig. 4. We merged the data of FRT a and b because there was no significant difference between them. We found that STN-DBS significantly reduced the FRT time in the DBS side; however, it never reached the normal level ($F = 578.753$, $P = 0.000$, $df = 539$). However, L-dopa achieved full recovery because no significant difference was found between the L-dopa test and normal control ($F = 0.520$, $P = 0.474$, $df = 1259$). These data reproduced the results in our previous study (Asakawa et al., 2012).

These abovementioned results confirmed the stability and reliability of our experimental system.

3.2 Verification of the performance of GT affected by treatments of L-dopa and DBS

Fig. 5 presents the representative video frames in a PD monkey model (monkey 2). The total gripping time was 2.36 s when DBS was off and 1.98 s when DBS was on, whereas it was 0.24 s when undergoing L-dopa administration. The gripping time of a normal monkey was 0.30 s. From the video captures, we did not find any changes in the gripping pattern in PD monkeys. This is different from the spinal injury monkey model in which the gripping pattern was remarkably abnormal (Nishimura et al., 2007). The only change in the gripping motor in PD states is the speed, which is slower than healthy animals.

Fig. 6 presents the performance of GT affected by the treatments of L-dopa and DBS.

After the L-dopa administration, the gripping time reduced to a normal level ($F = 1.446$, $P = 0.232$, $df = 1259$, L-dopa vs. Normal control) ($F = 1995.330$, $P = 0.000$, $df = 359$, L-dopa vs. DBS on). The slowness of the gripping motor in PD monkeys can be fully recovered by L-dopa administration. Interestingly, despite DBS showing the tendency to reduce gripping time, it could not achieve a significant improvement ($F = 3.041$, $P = 0.084$, $df = 359$).

4. Discussion

In this study, we developed a novel behavioral assessment to evaluate the precision grip motor ability in monkeys, namely, GT, measuring the slowness of the precision grip in PD state, which is a complete result of rigidity and bradykinesia (Mirabella et al., 2013). Similar to the FRT, GT can also be attributed to a "food reach behavior," which is derived from the natural feeding drive in animals. Hence, animal training is quite simple. To the best of our knowledge, it is the most straightforward objective tool to

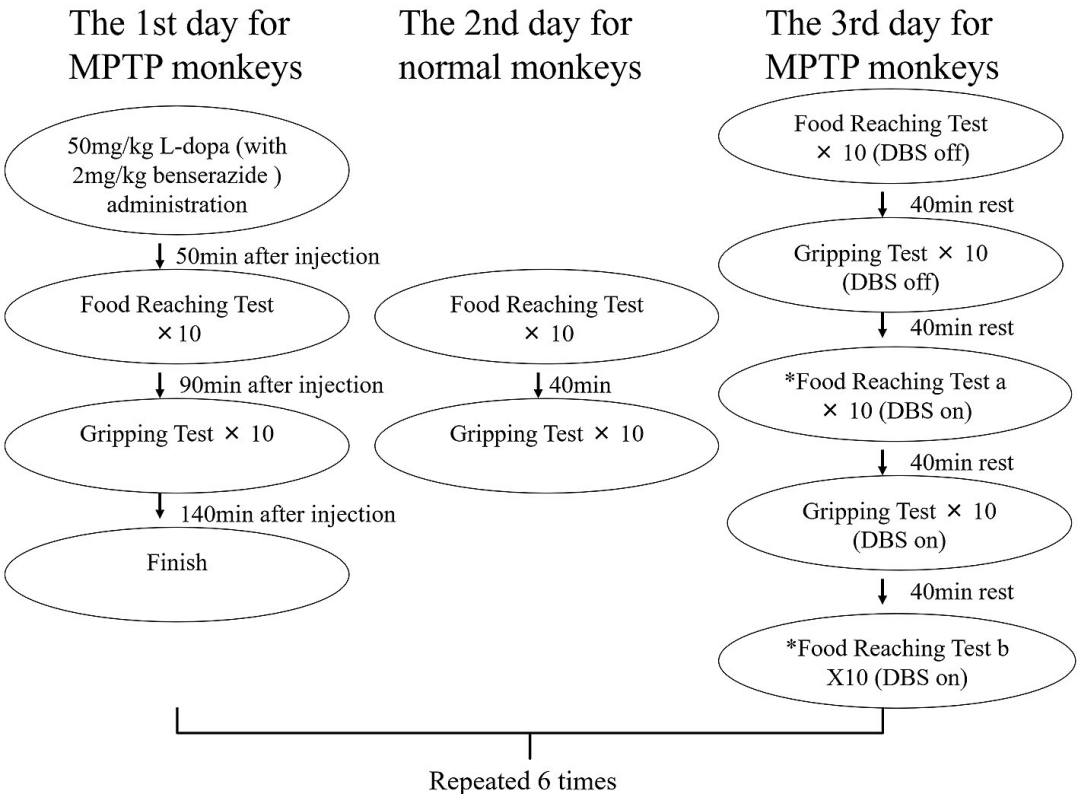

Figure 2. The experimental design of this study. L-dopa test was performed in MPTP-treated monkeys on the first day. Food reaching test (FRT) was performed, followed by the gripping test (GT) after L-dopa administration. FRT and GT were performed in normal (healthy) monkeys on the second day. The third day was for MPTP-treated monkeys. FRT and GT were performed when DBS was off, and then DBS was on in MPTP-treated monkeys. For confirming the stability of the experimental system, FRT and FRT b were performed before and after GT, respectively.

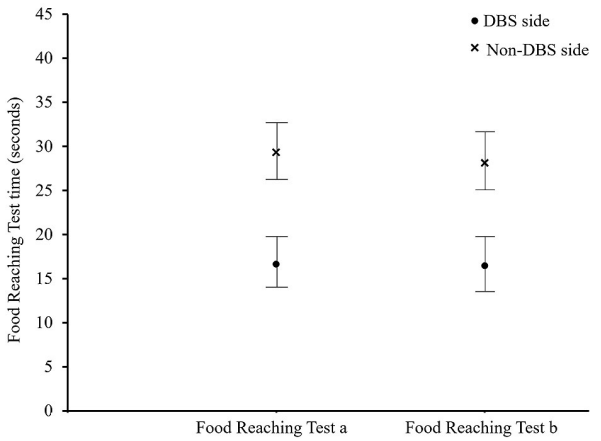

Figure 3. The results of FRT before and after GT. There was no significant difference in the FRT time before (FRT a) and after (FRT b) GT, both in the DBS and non-DBS sides. The stability of the DBS system was confirmed.

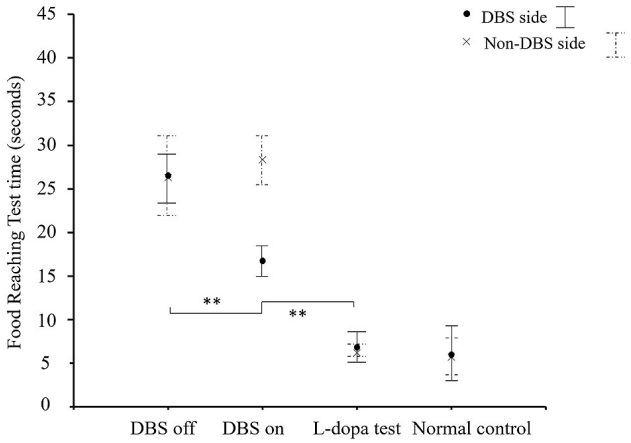

Figure 4. The results of FRT affected by treatments of L-dopa and DBS. STN-DBS reduced the FRT time significantly; however, it never reached a normal level. L-dopa test can improve the FRT time to a normal level. $^{**}P < 0.01$.

measure the finger fine motor ability in PD monkeys. We believe it is useful for researchers investigating the state of fine motor skills in PD monkeys.

Our previous study had verified the utility and reliability of FRT (Asakawa et al., 2012). Employing parallel experiments of FRT and GT affected by L-dopa administration and STN-DBS, the utility of GT was also verified. First, the DBS system in this study was stable because no difference was found between the FRT time before and after GT (FRT a vs. FRT b; $P > 0.05$) (Fig. 3). Then, the experimental system was reliable because we reproduced the results of FRT in our previous study (Fig. 4). Thus, verification of GT using the present experimental system is reliable.

Figure 5. The representative video frames in one MPTP-treated monkey (monkey 2) along with a normal (healthy) control monkey. Frames with an interval of 0.18 s (six flames) when DBS was on and off, and an interval of 0.06 s (two flames) when performing the L-dopa test were listed. The gripping pattern in PD monkeys was similar to the healthy monkeys, except for the gripping speed.

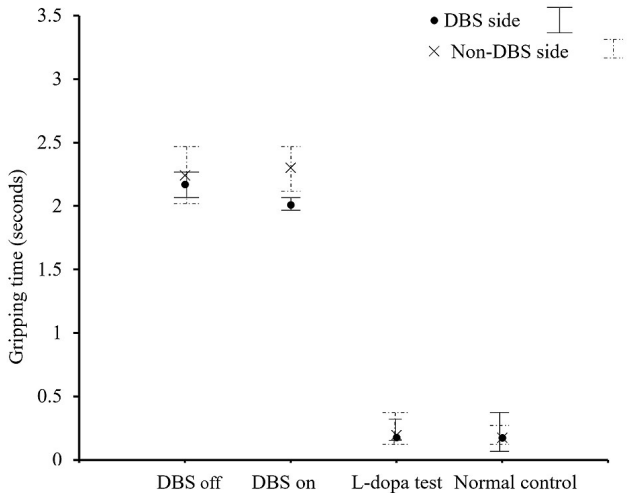

Figure 6. Performance of GT affected by the treatments of L-dopa and DBS. No significant difference in gripping time was found between healthy and PD monkeys that underwent L-dopa administration. DBS did not achieve significant improvement in gripping time in PD monkeys.

One critical result was that the L-dopa administration achieved full recovery of GT. We found that there was no significant difference in the gripping time between healthy and PD monkeys undergoing L-dopa treatment (Fig. 6). It has been well documented that fine motor can be remarkably ameliorated by L-dopa administration (Taylor Tavares et al., 2005; Van Vugt et al., 2013; Wenzelburger et al., 2003). Our present and previous studies employed a hefty dose of L-dopa (50 mg/kg) to achieve full recovery. Such full recovery was presented entirely, both in FRT and in the new GT. The utility of the GT was therefore verified.

Another interesting finding was that STN-DBS improved the gross motor ability measured by FRT, but not the fine motor ability measured by GT (Fig. 6). The previous studies concerning the efficacy of DBS on fine motor resulted in controversial conclusions. Wenzelburger et al. (2003) found that the efficacy of STN-DBS is not as good as that of L-dopa administration in treating the dysfunction of precision grip in PD patients. Later, Gorniak et al. (2013) came to a similar conclusion that bilateral STN-DBS was good for alleviating gross motor dysfunction but did not provide the same magnitude of benefit to fine motor coordination. However, other authors obtained an adverse conclusion. Taylor Tavares et al. (2005) reported that bilateral STN-DBS significantly improves fine motor control. Nakamura et al. (2007) performed STN-

DBS and DBS in globus pallidus internus in 33 PD patients and found that DBS of these 2 targets has the same efficacy in improving hand movements. Our previous clinical study also suggested DBS before dopaminergic medications to improve the dexterity in PD patients (Nozaki et al., 2018). We suggest that the divergence of these findings might be caused by the following reasons:

(1) The behavioral assessments employed for the fine motor. Many studies, including our previous study (Nozaki et al., 2018), employed conventional tasks like BBT for evaluating the fine motor, which commonly requires the patient to grasp the cubes or blocks from one compartment and subsequently release it into the other compartments. The motor "to grasp the cubes" and then "to release them" is not only simple precision grip motor skills that only involved fingers but also includes the movement of the wrist and elbow. However, such movements cannot be simply attributed to fine motor skills and are much more time-consuming than the gripping motor. Regarding the results of this study in monkeys, the FRT time in monkeys (gross motor) was over 5 s (Fig. 4), which could be measured by a stopwatch by eyes. The gripping time was around 2 seconds in the PD monkey and around 0.30 s in a normal (healthy) monkey, which could not be measured by eyes (Fig. 5 and 6). It is possible that the results of tasks like BBT were mainly confused by the gross motor skills that involved the wrist and elbow. To precisely measure the precision grip of the finger in humans, novel tasks that are analogous to GT in monkeys are required. Our lab is now developing the GT for humans.

(2) The different DBS parameter setting. Our previous study in the rodent model suggested that the most optimal parameter setting for the amelioration of various symptoms is different (Fang et al., 2010). Understandably, the most appropriate parameters to achieve the best efficacy for gross motor skills might be different from those for the precision grip of the finger. We used the same parameters setting as our previous study, namely "*the lowest current intensity to stop tremor*" (Asakawa et al., 2012). However, these parameters might not be optimized for motor function. In the future, we aim to verify the effects of DBS on finger fine motor skills, selecting the most optimized parameters for the motor function beforehand. Moreover, performing the L-dopa test after DBS is also interesting, which could be included in future work.

(3) The stimulation targets. The subtle target location within STN may cause different efficacy between gross motor skill and fine motor skill. We believe that the underlying mechanisms are quite complex and multifold, which are not fully understood. The verification of these hypotheses from multiple dimensions requires further investigation.

Here, GT was developed using the same equipment used in FRT. We are now attempting to combine GT with FRT and developing a multipurpose tool to simultaneously measure the gross motor and finger fine motor during one experiment (Asakawa et al., 2016a). As a task mainly designed for monkeys, the most challenging procedure is to train the monkey to be accustomed to the experimental system. This step is somewhat difficult and time-consuming in MPTP-treated monkey since, in our previous study, we verified the reduction of the learning ability in the PD animal model (Fang et al., 2006). Thus, the simplification of these tasks is important for future work. Moreover, such GT is also applicable to human patients. We are now developing GT using an analogous system for humans.

5. Conclusions

Here, we developed a novel GT for the assessment of the precision grip motor ability of the finger in PD monkeys. We found that gross motor ability assessed by FRT could be improved using treatments of both L-dopa and DBS. The finger fine motor ability measured by this novel GT could be ameliorated by the L-dopa medication, but not by STN-DBS. These results verified the utility of GT, which is a simple, convenient, and objective task to evaluate the finger fine motor ability in the PD monkey model. The mechanisms of the efficacy of DBS on fine motor skills require further investigation.

Author contributions

TA contributed the original ideas and designed the study. SK, TA, TN, KS, TS, and KK performed the operation. SK, TA, TN, and KK performed the behavioral test. SK and TA analyzed the data and ran the statistics. SK and TA wrote the first draft. KK checked the data and critically reviewed the manuscript. All authors approved the final version. TA and KK supervised the study.

Ethics approval and consent to participate

All monkeys were treated as per the Guidelines for the Care and Use of Laboratory Animals of the National Institute of Health. All experiments were approved by the Animal Care and Use Committee of Hamamatsu University School of Medicine (permission number 2011051).

Acknowledgments

This work was supported by grants from the Japan Society for the Promotion of Science (Grant-in-Aid for Young Scientists, Type B, No. 20791025, and Grant-in-Aid for Scientific Research C, General, No. 24592157,15k10358 and 18K08991).

The authors would like to thank Enago (https://www.enago.jp/) for the English language review.

Conflict of Interest

The authors declare no conflicts of interest in the present study.

Submitted: May 20, 2020
Revised: June 15, 2020
Accepted: June 19, 2020
Published: xxxx, 2020

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