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A psychophysical and electrophysiological platform using internal action selection task in primate parkinsonian model *

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Abstract— **Internal action selection is an important motor control, in which patients with Parkinson's disease (PD) generally show deficiencies. Basal ganglia (BG) is proved to play an important role in decision-making and act as a specialized internal selection device within the vertebrate brain architecture. Furthermore, some studies showed there was a close relationship among striatal dopamine signaling, action selection and time interval by training mice to perform an internal selection task. However, the neural mechanism of the internal action selection is still unclear.**

In this study, we setup a platform for psychophysical and electrophysiological study and recorded behavioral data from normal human subjects and primates when they performing an internal action selection task. The results showed that longer trial intervals led to longer action transition time, which indicates the time interval biases internal action selection, and the effect of movement direction was not significant. Furthermore, we recorded the task-related neuronal activity in primate's primary motor cortex (M1). Preliminary data showed there were significant firing rate changes in M1 at the transition of action selection.

I. INTRODUCTION

When PD patients draw a V shape, they can draw the line going down just fine or the line going up just fine. But they have major difficulty making the switch from one direction to the other and spend much longer at the transition. This defect in motor control and behavior selection highlights the importance of BG circuits in decision-making and motor behavior organization [1].

Jin et al. studied the activity of BG neuronal pathways during the learning and execution of sequential movement aiming to explore the effect and mechanism of BG on action organization. They found that there was start / stop neuron in the basal ganglia loop [2, 3]. Then, they trained mice to discriminate two time intervals and respond on either the left or right lever accordingly [4]. The retraction of the left and right lever prompted the initiation of the experiment, two levers were retracted for either 2 or 8 s (50% chance of either interval, random order). Both levers were then extended and the first response on the left lever following a 2 s retraction interval or the first response on the right lever following an 8 s retraction interval resulted in reward delivery. Specifically, animals were initially biased toward the short-duration option, neutral at the midpoint of short-duration and long-duration, and biased to the long-duration option at later time points. When the mice performed the task, dopamine (DA) was recorded by fast-scan cyclic voltammetry with optogenetic stimulation in the compact part of substantia nigra [5]. They concluded that DA biases action selection.

Time flies when you are happy, and days of sorrow are like years. Midbrain DA neurons are implicated in many of the psychological factors [6] and disorders [7, 8, 9] associated with changes in time estimation. Manipulations of the DAergic system by pharmacological [10] or genetic [11] approaches could disrupt timing behavior, suggesting that DA neurons may directly modulate timing. In some cases, DA seems to speed up timekeeping [10, 12], and in others, DA seems to slow down or not affect timekeeping [13, 14]. Soares et al. measured and manipulated the activity of DA neurons in mice as they performed categorical decisions about duration [15] and concluded that DA directly modulates time estimation, which lead to bias action selection.

Previous researchers showed that time interval can influence mice's action selection. In this study, we designed an adopted version of a temporal bisection task for human subjects and non-human primates according to previous experimental paradigm. We intended to answer the question whether there is a similar effect in humans and non-human primates, which task interval biased mice's action selection in previous studies. We recorded the task-related electrophysiological data of primary motor cortex (M1) in primates for finding the electrophysiological changes of M1 at the transition time of action selection. Undergoing degeneration in PD result in severe deficits in self-initiated action selection and voluntary movement control [16]. We tried to explore the gradually effect of PD during internal action selection in primate parkinsonian model with this psychophysical and electrophysiological platform.

II. MATERIALS AND METHODS

A. Experimental object

Human subjects: 12 right-handedness subjects (male: 6; female: 6) aged 20~25 years old with normal state of intelligence and health.

Non-human primates subjects: 2 monkeys (monkey X: male, weight 9.0 kg, right-handedness; monkey N: male, weight 7.5 kg, left-handedness) were trained to perform the internal selection task with their dominant hand. The monkeys' health was monitored by a veterinarian, and their fluid consumption, diet, and weight were monitored daily. All procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals

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(1996) and with the Hebrew University guidelines for the use and care of laboratory animals in research and were approved and supervised by the Institutional Animal Care and Use Committee.

B. Experimental platform

We presented the experiment task on the touchscreen by the control system (Monkeylogic toolkit based on Matlab), collected the behavior data for human subjects and monkeys, and the M1 neuron signal recorded only for monkeys by electrophysiological data acquisition systems (OmniPlex) (Fig. 1).

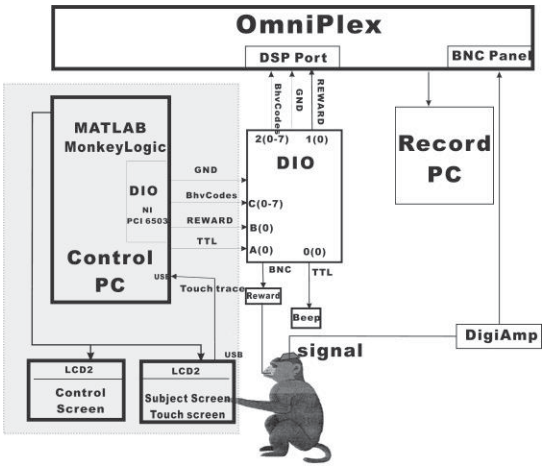

Figure 1 Diagram of experimental platform: complete experimental platform for monkey subjects and shadow part of lower left corner for human subjects.

C. Internal selection task

Subjects were asked to perform an adopted version of a temporal bisection task by hand and monkeys needed to sit in a chair. They were trained to distinguish short interval of 2 s and longer intervals of 3, 4, 6 or 8 s between Center off and Target on to predict the location of the target. Using long interval of 4 s as an example, each trial initiated with the appearance of a green circle on the center of the touchscreen with the radius of 1.5 cm and a small green circle on the left of the touchscreen with the radius of 0.5 cm (or red square on the center of the touchscreen with the side length of 3 cm and a small red square on the right of the touchscreen with the side length of 1 cm), then subjects needed to touch the center circle (or square) within 4 s. Once the touchscreen detected the center circle (or square) had been touched, those two circles (or squares) disappeared. After that, two kinds of trials with 2- or 4-s intervals were randomly interleaved with equal probability. A green circle target with the radius of 1.5 cm appeared at 10 cm left to the touchscreen center (or a 3 cm red square target at 10 cm right to the center) following a 2 s interval (short interval trial). In long interval trial, a green circle target appeared at 10 cm right to the touchscreen center (or a red square target at 10 cm left to the center) following a 4 s interval (Fig. 2). The subjects were asked to predict the location and wait at either right or left to the center for the target onset, so they were able to touch the target as soon as possible. Monkeys got rewards if they touched the target within 200 ms after the target onset. After training, their hand moved from left to right at the transition time in condition 2 and moved from right to left at the transition time in condition 4.

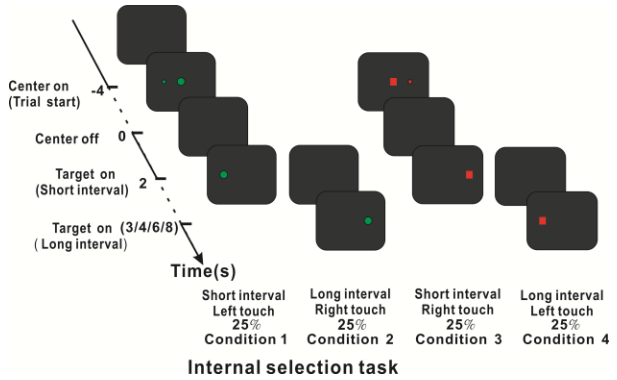

Figure 2 Task design of the internal selection task: 25% chance of each condition, random order.

D. Surgical procedures

After initial anesthesia with ketamine 10 mg/kg intramuscular injection, the monkeys were generally anesthetized with isoflurane (2%-3%) during the surgery by endotracheal intubation and were placed in a stereotactic frame. The animals' welfare was monitored throughout the surgery by a trained veterinarian and an unconsciousness state was maintained.

Lateral ventricle operation for developing the PD monkey with intracerebroventricular 1-methyl-4-phenylpyridine (MPP^+) injections [17]: The coordinates of the right ventricle of the monkey X were located at 18 mm in front of the A/P zero location, 1.5 mm right to the median sagittal line, and 17 mm beneath the skull. A sterile pipe made of stain-less steel held on an electrode manipulator attached to the stereotaxic instrument was inserted vertically into the ventricle. The final depth of the implanted pipe was determined by cerebrospinal fluid spilling from the top of the pipe. One week after surgery, quantitative MPP^+ (0.2 ml, 0.67 mg/ml) were injected in the lateral ventricle of the monkey sitting in the monkey chairs with a syringe via a plastic hose three times a week. Video recordings of monkeys' behavior were collected once a week (Tuesday afternoon between 12:00 and 13:00, including lunch time) and evaluated for Parkinsonian symptoms using part A of the Kurlan scale, which utilizes seven important measures of PD [18].

Electrode implantation: We performed occipital craniotomy from 2 mm to 18 mm in front of the A/P zero location, from 4 mm to 20 mm left to the median sagittal line and exposed M1 located at 12 mm in front of the A/P zero location, 15 mm left to the median sagittal line [19]. A Utah Array (Blackrock ICS-96, electrode length: 1.5 mm) [20] was implanted into M1 with the Blackrock Electrode Inserter System (PSI: 20; Pulse: 3; Implantable electrode length: 1.5 mm). The connector of Utah Array and the outside part of sterile pipe implanted into the ventricle were protected by a chamber equipped with a protective cap. During surgery, to prevent excessive intracranial pressure, mannitol was administered intravenously. The monkeys' head need to be immobilized during the recording of the neural signals, so we implanted a fixation post on top of the monkey's skull. One

week after surgery, the neuronal data can be collected through the electrophysiological data acquisition systems.

After the operation, the monkey was intramuscularly injected with Penicillin for three days.

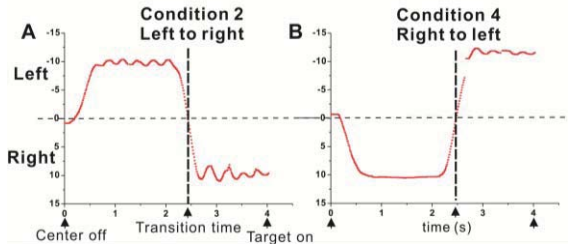

Figure 3 A: The time-variation horizontal distance (cm) from hand touch point to the center of the screen when one subject performed condition 2 of internal selection task and the movement direction is right to left at transition time; B: The time-variation horizontal distance from hand touch-point to the center of the screen when one subject performed condition 4 of internal selection task and the movement direction is left to right at transition time.

III. EXPERIMENTAL DATA

We recorded behavioral data about the transition time (Fig. 3) of 12 human subjects and monkey N corresponding to different long time intervals with intervals spanning 3s, 4s, 6s and 8 s (Tab. 1) in condition 2 of internal selection task and the transition time of 11 human subjects and 2 monkeys corresponding to different direction with movement direction from left to right and from right to left (Tab. 2).

Table 1
Transition time (s) (Fig. 3) of subjects in the different long time intervals

	Long intervals			
	3 s	**4 s**	**6 s**	**8 s**
Subject 1	2.544	3.158	3.308	3.703
Subject 2	2.524	2.828	3.467	4.226
Subject 3	2.733	2.979	3.738	3.473
Subject 4	2.432	2.633	3.185	3.141
Subject 5	2.411	2.567	3.207	3.550
Subject 6	2.541	2.796	3.423	4.624
Subject 7	2.680	3.197	3.823	4.283
Subject 8	2.583	2.906	3.215	3.694
Subject 9	2.510	2.854	3.648	3.836
Subject 10	2.632	2.517	3.055	3.157
Subject 11	2.628	3.365	3.939	4.249
Subject 12	2.513	2.798	2.996	3.807
Monkey N	2.537	2.983	3.618	4.448

Table 2
Transition time (s) of subjects in the different direction

	Movement direction at transition time (Fig. 3)	
	Left to right	**Right to left**
Subject 1	3.157	2.961
Subject 2	2.827	2.764
Subject 3	2.978	3.138
Subject 4	2.633	2.674
Subject 5	2.567	2.979
Subject 6	2.796	2.862
Subject 7	3.196	3.099
Subject 8	2.905	2.835
Subject 9	2.854	2.967
Subject 10	2.516	2.527
Subject 11	3.365	3.353
Monkey N	3.003	3.111
Monkey X	2.983	2.940

Then, we explored the task-related M1 neuronal data changes of monkey X at transition time of action selection.

IV. EXPERIMENTAL RESULT.

A. Behavioral data

Time interval: This experimental task included condition 1 and condition 2 of internal selection task interleaved randomly with equal probability (Fig. 2). After practicing, subjects acquired this task quickly and reached a correct rate >85% with the specific strategy of subjects performed long interval experiment was that they were initially biased toward the short-interval (2-s interval) option and biased to the long-interval option after they had estimated the interval over 2 s. The touchpoint of the subjects' hand on the touchscreen was recorded by the behavioral data acquisition system during the whole process of trial. We mainly analyzed the horizontal components of subjects' hand movement (Fig. 3). The transition time changes of 12 human subjects and monkey N corresponding to the different time intervals showed that longer intervals led to longer transition time (Fig. 4A, B), which was similar results obtained on humans, monkeys and mice. However, the transition time was not always at the midpoint of short interval and long interval on our subjects, which was different from the result on mice [5].

Direction: This experimental task included all conditions of internal selection task interleaved randomly with equal probability (Fig. 2). Considering the concentration time of monkeys, we set long interval to 4 s researching the effect of direction. The main difference between condition 2 and condition 4 of internal selection task was movement direction at transition time (Fig. 3). The subjects of this experiment included 11 human subjects and two monkeys. The behavioral data showed that the effect of direction on transition time was not significant in mean value of human subjects and monkeys (Fig. 4C, D). Direction had a

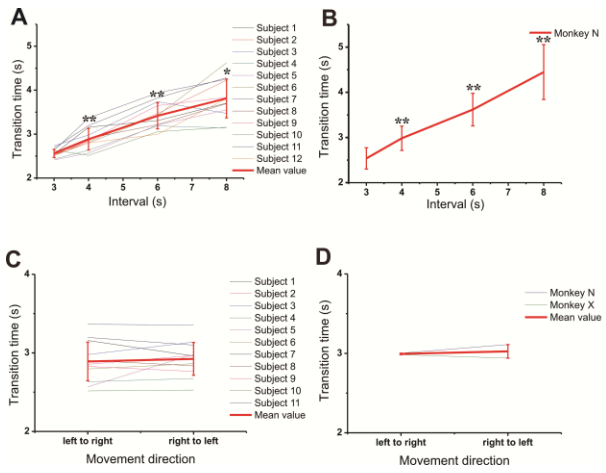

Figure 4 A: The transition times of 12 human subjects and their mean value with long interval spanning 3, 4, 6 and 8 s; B: The transition times of monkey N with long interval spanning 3, 4, 6 and 8 s; C: The transition times of 11 human subjects and their mean value corresponding to different movement direction with setting long interval to 4 s; D: The transition times of two monkeys and their mean value corresponding to different movement direction with setting long interval to 4 s.
**: T-test P value <0.01; *: T-test 0.01< P value < 0.05

significant effect on the transition time of each individual, and individual differences were obvious, which might be related to the inconsistent speed of each individual's left and right movements.

B. Neuronal data

In the process of data acquisition, we set up some event markers in each trial to align the neurophysiological data with the behavioral data. Interestingly, the data suggested that some M1 neurons showed an increase in firing rate at transition time and some M1 neurons showed a decrease in firing rate at transition time (Fig. 5).

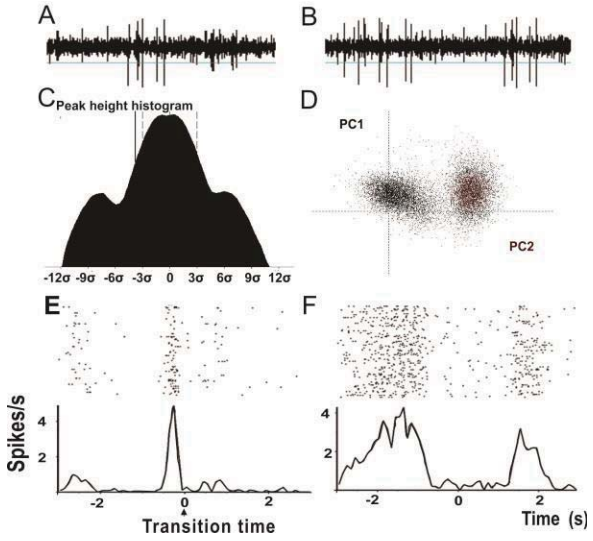

Figure 5 A, B: The original neurons signal collected by the electrophysiological data acquisition systems with a signal-to-noise ratio more than 3; C: Peak height histogram; D: PCA analysis of signal and noise; E, F: The peristimulus time histogram (PSTH) of M1 neuron aligning to transition time (0 s).

V. DISCUSSION

Previous studies had shown the relationship between BG and internal action selection, but few directly investigated neural signals related to action selection in M1. Our platform can be used to record M1 neuronal data in experiment with long time interval variation and explore some manifestations of action transition time in M1 neurons. We expect to find M1 neurons that are involved in internal action selection. Furthermore, we will develop PD primate model by MPP^{+}, which is expected to study the changes of task-related internal action selection and M1 neuron activity in primates at different developing course of PD.

Does the nigrostriatal dopamine exerts its effect on action selection at the sensory input or at the decision-making level? There is no definite conclusion. Action selection is a competitive mechanism. We design the internal selection task to avoid the perturbation of external stimulation, and the development of PD will affect the concentration of dopamine in the middle brain of primate, which makes it possible to investigate the direct influence of the nigrostriatal dopamine on M1.

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