The abridged version of the doctoral thesis

Title: **Cortical control of subthalamic activity through the hyperdirect and indirect pathways in monkeys**

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Introduction

The subthalamic nucleus (STN) plays a key role in the control of voluntary movements and basal ganglia (BG) disorders, such as Parkinson's disease and hemiballismus (Bergman et al. 1994, Hassani et al. 1996, Galvan et al. 2008). It is known that lesion, chemical blockade or deep brain stimulation (DBS) of the STN is an effective treatment of movement disorders (Bergman et al. 1990, Aziz et al. 1991, Pollak et al. 1993, Benabid et al. 1994, Limousin et al. 1995). The STN receives glutamatergic inputs directly from the cerebral cortex and gamma-aminobutyric acid mediated (GABAergic) inputs from the external segment of the globus pallidus (GPe), which are mediated by the cortico-STN *hyperdiret* (Monakow et al. 1978, Nambu et al. 1996, Nambu et al. 2000, Nambu et al. 2002) and cortico-striato-GPe-STN *indirect* pathways (Alexander et al. 1990), respectively. Then, the STN drives the internal segment of the globus pallidus, the output nucleus of the BG (Jaeger et al. 2011). Thus, it is important to clarify how STN neuronal activity is controlled by these inputs.

Previous studies demonstrated that cortical stimulation induced biphasic response in STN neurons, which is composed of early and late excitations, interposed by a short gap (Nambu et al. 2000). The origin of that biphasic response is still not clear in monkeys. In the present study, we considered two possibilities of the origin of biphasic response in the STN induced by cortical stimulation. 1) Early and late excitations are mediated by the *hyperdirect* and *indirect* pathways, respectively, which was shown in anesthetized rats' experiments. 2) Cortically induced long excitation is intervened by the inhibition from the GPe through Cx-STN-GPe-STN transmission. Thus, the first goal of the present study is to investigate the origin of each component of the biphasic response in the STN induced by cortical stimulation in awake monkeys. The second goal of the present study is to

examine the control mechanism of STN spontaneous activity through the *hyperdirect* and *indirect* pathways: the former inputs to the STN are glutamatergic and the latter inputs are GABAergic.

In the present study, I also made an attempt to clarify neuronal substrates of voluntary movement control. The classical model of BG (DeLong 1990, Mink 1996) suggests that STN implements excitatory influence on the basal ganglia output nuclei, which inhibit the thalamus and the cortex. Studies of the STN in animals and humans demonstrated its activation during movement inhibition (Aron et al. 2006, Ray et al. 2012, Schmidt et al. 2013, Bastin et al. 2014). The STN activity was reported to play a key role in action suppression (Frank 2006, Li et al. 2008, Sharp et al. 2010, Fife et al. 2017, Pasquereau et al. 2017). The signals through the *hyperdirect* and *indirect* BG pathways are considered to be able to block activity responsible for motor initiation that transmits through the *direct* pathway (Mink 1996, Nambu et al. 2002, Nambu 2004). Moreover, there is evidence that STN activity is modulated in relation to the motor planning and voluntary limb movements (Alexander et al. 1990, Fischer et al. 2017, Zavala et al. 2017). Thus, I hypothesize that a subdivision of STN neurons might be involved in motor program execution and cancellation. In this study, I made an attempt to clarify the functions of the STN in the information processing and integration during motor task performance. The third goal of the present study is to clarify the involvement of STN neuronal activity in voluntary movement control.

Materials & Methods

Three female Japanese monkeys (*Macaca fuscata, Monkey K8, K9, and S*) were used in this study. *Monkey K8, K9* were used for simulation study, and *Monkey S* for behavioral study. Each monkey was trained to sit in a primate chair quietly. *Monkey S* was trained to perform goal-directed reaching task with delay using its right upper limb in order to investigate the role of the STN in voluntary movement control.

The goal-directed reaching task with delay combined two paradigms: the “Stop” signal task and the “Go/NoGo” task. In the present study was used a touch panel with three slots (Left, Center, Right). In the bottom of each slot a two-color (green and red) light-emitting diode (LED) was installed. The task includes three types of trials: “Go”,

"Stop" and "NoGo". In "Go" trials after the triggering signal (S2; LEDs lit by green color), the monkey was required to perform reaching movements (hand release, HR; finger in, FI) to the target, which was indicated by an instruction signal (S1; one of LEDs lit by red color) to get the reward (RW). In "Stop" trials, same types of instruction signals were presented as in "Go" trials, however, the triggering signal was different (LEDs lit by red color) and indicated stopping of action. In "NoGo" trials, from the beginning the monkey was informed by instruction signal (LEDs lit by red color) that movement performance is not required.

After the chair training (*Monkeys K8 and K9*) and task training (*Monkey S*), monkeys received aseptic surgical operation to fix their head painlessly in a stereotaxic frame attached to a monkey chair. After full recovery from the operation, the skull over the primary motor cortex (MI) and supplementary motor area (SMA) was removed under anesthesia with ketamine hydrochloride (10 mg/kg, im) and xylazine hydrochloride (1-2 mg/kg, im). Electrophysiological mapping was performed and the forelimb regions of the MI and SMA were identified by recording neuronal activity in response to somatosensory stimuli and observing body part movements evoked by intracortical microstimulation. After mapping, two pairs of bipolar stimulating electrodes (enamel-coated stainless steel wires, 200 μm diameter; 2 mm intertip distance) were implanted chronically into the distal and proximal forearm regions of the MI, and one pair into the forearm region of the SMA. Animals were administered antibiotics, steroids (dexamethasone), and analgesics after the surgical procedures.

Recordings of neuronal activity were started after full recovery from the second surgery and was performed two or three days per week for several months. During the experimental session, the monkey was seated in a primate chair with head fixed in the frame, leaving body and limbs free to move. Recordings were conducted while the *Monkey K8, K9* were awake and *Monkey S* performed the task. Using a hydraulic Microdrive, a glass-coated Elgiloy microelectrode (0.7–1.5 MΩ at 1 kHz) was penetrated vertically into the STN. The amplified and filtered unitary STN activity was recorded. In order to confirm the location of the STN, in addition to mid-frequency (20 - 40 Hz) firings of neurons and responses to passive joint movements, responses to cortical stimulation were verified. Peri-stimulus time histograms (PSTHs; 1 ms bin, summed for 100 stimulus trials) were constructed to examine responses to electrical stimulation through the

electrodes implanted in the MI and SMA (bipolar stimulation, 300 μs duration, single pulse, strength of 0.5-0.7 mA and interval of 1.4 s).

Single-unit recordings in combination with local applications of drugs into the vicinity of recorded STN neurons were performed in the present study. The silica tubes were attached to the recording glass-coated Elgiloy microelectrode and connected to two 25-μl Hamilton microsyringes, which contained two of the following drugs dissolved in saline: 1) CPP – NMDA receptor antagonist; 2) NBQX – AMPA/kainate receptor antagonist; 3) a mixture of CPP and NBQX; 4) gabazine – $GABA_A$ receptor antagonist. When STN neurons were responded to MI and/or SMA stimulation, a total volume of 0.2 - 0.6 μl of each drug was injected at a rate of 0.03-0.05 μl/min. In the control state and after drugs injections PSTHs and autocorrelograms (0.5 ms bin width) for spontaneous activity (digitized recording for 50 s) were constructed. I also confirmed that injections of saline alone did not alter the spontaneous firing rates and patterns and the cortically induced responses of STN neurons.

Single-unit recordings of STN neurons in combination with broad applications of drugs into the putamen or GPe were done in *Monkey K8* and *K9*. First, the forelimb region of the putamen or GPe was identified. A 10-μl Hamilton microsyringe with attached Teflon-coated tungsten wire (bare diameter, 50 μm) for recording and stimulation was inserted obliquely into the forelimb regions of the putamen or GPe. The following drugs dissolved in saline were injected: 1) muscimol – $GABA_A$ receptor agonist; 2) NBQX; 3) gabazine. The recording from the STN was performed using glass-coated Elgiloy microelectrode as described above. When STN neuron responded to cortical stimulation, the neuronal response to the putamen or GPe stimulation (bipolar stimulation, 300 μs duration, single pulse, strength of 0.1 - 0.7 mA, sometimes up to 1.0 mA and interval of 1.4 s) was examined, and a total volume of 1.0 - 4.0 μl of the drug was injected into the putamen or GPe in the following combination: muscimol injection to the striatum to block striatal activity, muscimol injection to the GPe to block GPe activity, gabazine injection into the GPe to block putaminal GPe GABAergic neurotransmission.

Electromyograms (EMGs) were recorded two times for *Monkey S* using surface electrodes from the following muscles: wrist extensor, wrist flexor, biceps brachii, triceps brachii, trapezius, and deltoid.

Neuronal responses to the cortical stimulation and spontaneous firing rates and patterns were analyzed and compared before and after drug injection into the STN, putamen or GPe. Responses of STN neurons induced by cortical stimulation were evaluated based on PSTHs. The amplitude, duration, and latency of cortically evoked responses in the STN were analyzed before and after drugs injections. Amplitude was calculated as a number of spikes during the significant response minus that of the baseline discharge (mean). Duration of excitation or inhibition was defined as the period of significant response. Population PSTHs of STN neurons were constructed by averaging PSTHs of each neuron and smoothing with a Gaussian filter (σ = 10 ms) for each case of drugs injections.

Spontaneous firing rates and patterns were analyzed using continuous digitized recordings for 50 s. The following parameters were calculated: mean and SD of firing rates, mean, SD, and mode of inter-spike intervals (ISIs), burst index (BI) defined as the ratio of the mean of ISIs and the mode of ISIs, and coefficient of variation (CV) defined as the ratio of the SD of ISIs and the mean of ISIs. Spontaneous firing patterns were also analyzed by calculating autocorrelograms (0.5 ms bin width, for 50 s). The regularity of firing was assessed by the existence of multiple peaks and their height in the aotucorrelograms.

Paired, one-tailed *t*-tests were used to compare parameters before and after drug injections. Bonferroni tests were used to compare parameters of MI- and SMA-recipient neurons. $P < 0.05$ was considered significant.

The analysis of neuronal activity during the goal-directed reaching task with delay was performed to reveal the difference of the activity relative to different types of trials, task events, and targets before and after local drugs injections in the vicinity of recorded STN neurons. I examined response to cortical stimulation, and recorded activity of STN neurons, which receive cortical inputs from the forelimb area of the MI, during task performance. In the case of raster plots and population histograms in the behavioral task, neuronal activity was aligned separately according to the instruction signal (S1), triggering signal (S2), hand release from the resting position (HR), finger in the slot (FI) and reward (RW) timings for all types of trials, i.e., Go (Left, Center, Right), Stop (Left, Center, Right) and NoGo trials. Spike-density functions (SDFs) were calculated by smoothing the averaged activity with a Gaussian filter (σ = 10 ms). GABAergic and

glutamatergic components were calculated as subtraction of SDFs for successful trials before and after drugs injections:

GABAergic component = (SDF before gabazine) – (SDF after gabazine);

Glutamatergic component = (SDF before NBQX+CPP) – (SDF after NBQX+CPP).

In order to detect target- and event-related changes in SDFs and component (GABAergic, glutamatergic), the amplitudes of these functions relative to task events were calculated. The following calculations were performed for the functions aligned separately to each corresponding task event. The latency of significant changes was calculated in order to detect the timing of neuronal activity changes that related to the actual movement. It was defined as the time from the S2 presentation to the first amplitude of the largest neuronal response among three targets. Delay-, S2-, HR-, and FI-related activity were modulated by target directions. Directional selectivity (DS) of a neuron in each event was defined as:

$$DS = 1 - (|A_{med}| + |A_{min}|)/(|A_{max}| * 2),$$

where $|A_{max}|$, $|A_{med}|$, and $|A_{min}|$ are the absolute values of maximum, medium and minimum amplitudes among three targets (Left, Center, Right), respectively. DSs were calculated for both SDFs and component functions (GABAergic, glutamatergic). For each neuron, SDFs or component functions with the largest changes among three targets were selected for calculation of population activity.

I classified recorded STN neurons based on the components: 1) Positive or negative changes (polarities) of components, and 2) Presence or absence of the buildup activity during delay periods. I further classified STN neurons to following four groups based on the first criteria: I) Negative GABAergic and positive glutamatergic components; II) Positive GABAergic and positive glutamatergic components; III) Positive GABAergic and negative glutamatergic components; and IV) Negative GABAergic and negative glutamatergic components. According to the second criteria I picked up neurons with buildup activity during the delay period after S1 event for each component (GABAergic and glutamatergic, separately). DSs of each component at each task events were calculated.

EMG activity was analyzed using similar methods as applied for neuronal activity in task performance.

At the end of experiments, the recording and drug injection sites were marked by current injections (cathodal DC current of 20 μA for 30 s). Monkeys were deeply anesthetized with sodium pentobarbital (50 mg/kg, iv) and perfused transcardially with 0.1 M phosphate-buffered saline (pH 7.3), followed by 10% formalin in 0.1 M phosphate buffer (PB), and the same fresh buffer containing 10% sucrose and then 30% sucrose. The brains were removed and kept in 0.1 M PB containing 30% sucrose at 4°C, and then cut serially into 60-μm-thick frontal sections on a freezing microtome. These sections were mounted onto gelatin-coated glass slides and stained with 1% Neutral Red. The recording and drug injection sites were reconstructed according to the lesions made by current injections and the traces of the electrode tracks.

Results

A total of 158 STN neurons (79 neurons in Monkey K8; 79 neurons in Monkey K9) were recorded, and drug injections were performed in 91 STN neurons. Among them, 70 STN neurons were selected based on isolation criteria and presence of significant biphasic responses to cortical stimulation and analyzed in combination with drug injections into the STN (33 neurons), putamen (15 neurons) or GPe (22 neurons).

Cortical stimulation induced a biphasic response composed of early and late excitations, which were intervened by a short "gap" in STN neurons. In order to examine the origin of these biphasic responses, neuronal responses were compared before and after drug application into the basal ganglia. Local application of glutamatergic antagonists, especially NMDA receptor antagonist, into the vicinity of recorded STN neurons, diminished the early excitation among biphasic responses. Blockade of the striatum by local injection of muscimol, $GABA_A$ receptor agonist and blockade of the GPe by local injection of muscimol diminished late excitation. Blockade of the striato-GPe transmission by local injection of gabazine, $GABA_A$ receptor antagonist, into the GPe also abolished late excitation. These results suggest that cortically induced early and late excitation in STN neurons are mediated by the *hyperdirect* and *indirect* pathways, respectively, and that cortical inputs to the STN are mainly mediated by NMDA receptors.

I also examined the effects of local drug injection on the spontaneous firing rates and patterns. The spontaneous firing rates were changed after drugs injections according

to the predictions based on the BG circuitry model. There were no significant changes in BI and CV of STN spontaneous neuronal activity, except for the following cases: CV increase after gabazine injection in addition to NBQX+CPP injection into the STN; BI and CV increase after gabazine injection into the GPe. Significant changes of spontaneous firing patterns were observed after NBQX + CPP or gabazine injection into the STN, muscimol or gabazine injection into the GPe. These results suggest that spontaneous firing rates were continuously controlled by AMPA/kinate and NMDA glutamatergic and GABAergic inputs.

I recorded 115 STN neurons in *Monkey S* under the control state during the performance of goal-directed reaching task with delay. In the control state large portion of STN neurons demonstrated directional selectivity (DS) relative to Left, Center, or Right target in "Go" and/or "Stop" trials. The most of STN neurons changed their activity in relation to "Go" trials, and around 32% of them demonstrated stop-related activity. That suggests the involvement of STN activity in both motor execution and cancellation.

To explore the contribution of GABAergic and glutamatergic inputs to STN activity during task performance, I injected their antagonists (gabazine, NBQX+CPP) into the STN and observed STN activity in 23 neurons. The results showed that task-related STN activity was also controlled through direct glutamatergic and indirect GABAergic inputs from the cortex. Stop-related activity was mainly transmitted through the *hyperdirect* pathway that caused facilitation in the STN, while the role of the *indirect* pathway was minor. It was revealed that the buildup activity after the instruction signal was mainly caused by the glutamatergic component, however, in some neurons it also carried through the GABAergic input. In "Go" trials, GABAergic components showed longer latencies (240 ± 117 ms) than glutamatergic components (162 ± 104 ms). I revealed the direction selective (DS) activity in both "Go" and "Stop" trials, suggesting that some neurons with stop-related activity involved in a specific stop, while other neurons participated in a global stop.

The recorded STN neurons were found in the dorsal half of the STN, corresponding to the somatomotor region of the STN. Drug injection sites in the putamen and GPe were found in the dorso-ventral mid points in the GPe and putamen, also corresponding to the somatomotor region of the GPe and putamen, respectively.

EMG activity during task performance demonstrated significant activity changes in “Go” trials within the actual movement for wrist extensor, wrist flexor, biceps brachii, triceps brachii, trapezius, and deltoid in all target directions. In “Stop” and “NoGo” trials, no significant changes in EMG activity were detected. Thus, STN neuronal activity in “Stop” trials is not caused by muscles activity.

Discussion

The present results suggest that the STN receives direct information from the cortex, which is mediated through NMDA receptors, and contributed to the early excitation. The late excitation is originated from cortical information through the *indirect* pathway and GABAergic projections. These results largely agree with previous studies in rodents (Kitai et al. 1981, Rouzaire-Dubois et al. 1987, Fujimoto et al. 1993, Maurice et al. 1998). However, other rodent study reported the cortico-STN-GPe-STN transmission induced inhibition in the STN.

The biphasic response with a short gap between two excitations might be possible due to unique membrane properties of STN neurons that modulate action potentials quicker than in striatal neurons (Farries et al. 2010). Moreover, the conduction velocities of STN axons are faster than of striatal axons (Tremblay et al. 1989). These features of the STN makes it possible to be involved in the complex regulation of movement-related activity.

In the present study, I demonstrated the involvement of MI-receiving region of the STN in both motor program execution and cancellation. That observation agreed with studies on monkeys (Pasquereau et al. 2017) and humans (Benis et al. 2016). Moreover, the results suggest that task-related STN activity is also controlled through direct glutamatergic and indirect GABAergic inputs from the cortex. I revealed that stop-related activity is transmitted through the *hyperdirect* pathway while the *indirect* pathway shows minor function. According to the classic BG model, the role of the STN in stopping motor responses is realized by means of the inhibitory *indirect* pathway (Bogacz et al. 2007, Isoda et al. 2008). However, the idea of stop-related information transmission through the *hyperdirect* pathway was suggested previously based on human fMRI and single-unit recordings (Aron et al. 2016).

In the present study, stop-related activity was detected in the dorsolateral part of the STN (MI domain) according to the organization of cortico-STN inputs (Nambu et al. 2002). Previous reports showed involvement of the ventral region of the STN in stop action (Isoda et al. 2008, Bastin et al. 2014, Pasquereau et al. 2017) or stop-related activity in the dorsal area of the STN in humans (Benis et al. 2016). The role of MI-receiving territory of the STN in motor control has not been studied in details using primates or humans.

To sum up, our present data are consistent with the idea that the STN is a key structure of BG and plays important role in the control of voluntary movements and motor learning (Nambu et al. 2002, Hamani et al. 2004, Frank 2006). The conclusions of the present study are very important to understand not only the normal functions of the STN but also the pathophysiology of STN-related disorders and the therapy targeting at the STN. Lesions or applying high frequency stimulation in the STN ameliorates parkinsonian symptoms (Bergman et al. 1990, Aziz et al. 1991, Pollak et al. 1993, Benabid et al. 1994, Limousin et al. 1995). These procedures affect all components in the STN, such as afferent inputs through the *hyperdirect* and *indirec*t pathways and STN neuronal activity. If we can understand which component is most affected by such procedures, we may find more effective manipulating targets or methods to treat Parkinson's disease.

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