Involvement of human thalamic neurons in internally- and externally-generated movements

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Running title: Thalamic neurons and sequential movements
Abstract:

Several anatomical studies support the existence of recurrent neural pathways from cortical motor areas to the thalamus via basal ganglia and back to the cortex. Neuronal responses to internally- and externally generated sequential movements have been studied in the motor and premotor cortex of monkeys (Shima and Tanji, 2000), but the involvement of subcortical motor structures such as the thalamus have not been studied in monkeys or humans. We examined the activity of neurons during a sequential button press task in motor thalamus of parkinsonian as well as chronic pain patients undergoing implantation of deep brain stimulating electrodes. Single and dual microelectrode recordings were carried out during an internally generated task with a memorized sequence (MEM), and an externally driven task with the sequence given during task performance (FOLLOW). Average histograms of neuronal firing were constructed for each task and aligned with respect to visual cues (Ready, Go) or button presses (P1, P2, P3). Sequential movements were monitored with surface EMG and hand accelerometry, and cell responses were divided into movement-defined epochs for analysis of variance (ANOVA) and post-hoc means testing. Of 52 neurons tested, 31 were found to have task-related responses, and 10 were task-selective with 4 responding preferentially to MEM and 7 responding preferentially to FOLLOW (1 was both). Complex responses were found including preparatory, delay period, phase-, and task-specific activity. These kinds of responses suggest a role of the thalamus in both internally and externally cued arms movement and provide some evidence for a role in sequential movements.
INTRODUCTION

Sequential ordering of motor tasks is required for the simplest of daily activities such as writing, typing, and speaking. Individual neurons of the motor/premotor cortex (Tanji, 2001) appear to code the highly specialized aspects of planning and execution of sequential tasks. For example, monkey cortical neurons have been found to respond to the serial order of the elements (first, second, third) independent of the nature of a manual task (push, pull, turn) or direction of eye movement (Lu et al., 2002). Recordings of pallidal neurons in monkeys performing a remembered task and a tracking sequential task (Mushiake and Strick, 1995) revealed neurons responding preferentially during the memory task and just one of the three reaches, consistent with a role of the basal ganglia in the internal control and ordering of movements. Imaging studies in humans also indicate basal ganglia activation during the execution of sequential movements (Jueptner et al., 1997). Anatomical tract-tracing studies support the existence of recurrent neural pathways from the motor cortex to the thalamus via the basal ganglia (Alexander et al., 1990) termed ‘corticopallidothalamic loops’ which are implicated in motor as well as non-motor functions. However, few studies have examined the possible distributed nature of such responses in these recurrent pathways at subcortical levels, and none specifically in motor thalamus. Studies of thalamic neurons during stereotactic procedures typically are limited to determination of responses to passive and active arm movements and classification as “kinesthetic” or “voluntary”(Lenz et al., 1988). We wished to test responses during more complex tasks to determine if these known cell types had higher
level functions. We have now identified neurons in the human motor thalamus that respond during a sequential button press task with preparatory, delay-period, task and phase-specific activity, supporting a role for the motor thalamus in internally and externally generated movements.

METHODS

Stereotactic neurosurgery for implanting deep brain stimulating (DBS) electrodes in thalamus or subthalamic nucleus (STN) provided us with an opportunity to examine thalamic neurons during the performance of a sequential task. Single and dual channel microelectrode recordings (methods in (Lozano et al., 1996; Hutchison et al., 1998)) were made in the thalamus of 16 patients. Nine patients had Parkinson’s disease (PD) and underwent microelectrode-guided implantation of DBS electrodes in the STN in the OFF state (no drugs for 12 hours). Seven patients in the non-PD group had microelectrode-guided surgery targeting the thalamus for chronic pain (5), myoclonus (1), and essential tremor (1). The University Health Network Research Ethics Board approved these procedures and patients gave free and informed consent.

During the surgery, we recorded neuronal activity (n=52) as patients pressed a variable sequence of 3 of 5 buttons (P1-P3) in 2 types of visually guided tasks: an internally generated task with a memorized sequence (MEM) and an externally generated task where each cue was followed with a button press (FOL) (see Fig. 1a,b). During the MEM task, after the Ready LED illuminates, a 3-number sequence was presented by illuminating three of the buttons in sequence, and the patient had to remember this sequence until the Ready LED was extinguished (after 6s) signaling Go. The patient then reached to press the memorized sequence on the button pads. The patients returned their
hand to their chest between reaches. During the FOL task, no information was given to the patient between the Ready-Go period. The buttons to be pressed were indicated by illuminating one of the 5 buttons after the Go cue and following each successive button press. The MEM and FOL tasks consisted of 8 different sequences. These 8 sequences were: 213,231,235,245,453,435,431,421 to balance for direction-selective movements. Blocks of MEM and FOL trials were presented randomly. Contralateral electromyographic (EMG) activity of wrist extensors and flexors was recorded along with signals from an accelerometer attached to the back of the patient’s hand. The signals were recorded on analog videotape using a VR-100B digital recorder (Instrutech Corp., Port Washington NY) and analyzed off-line. To rule out the possibility that differences in neuronal responses between MEM and FOL tasks were due to different movements, we measured the reaction time (Go to P1) and the movement time (P1-P3) for the tasks. No significant differences in reaction or movement times were found between MEM and FOL tasks (T-test, P<0.05) (see Fig. 1c,d) and no significant difference was found between the PD patients and the other patients (P<0.05), likely because the task was slow-paced. Neuronal activity was examined in all trials for each cell and separated into 9 epochs based on the following movement cues and parameters: A) onset of Ready to Go cue when Ready LED extinguished; B) Go cue to movement onset; C) movement onset to end of first button press (P1); D) end of P1 to subsequent chest contact; E) chest contact after P1 to end of second button press (P2), F) end of P2 to subsequent chest contact; G) post-P2 chest contact to end of third button press (P3); H) end of P3 to chest contact; and I) post P3 chest contact to start of next trial with Ready LED. In cases where delay period activity was observed, an extra epoch “AA” was defined from end of
instruction LED to Ready cue off. Two way analysis of variance (ANOVA) was performed to examine the main effects of task and epoch and the interaction term task*epoch (SAS Software, Cary, NC) using a p value of 0.05. In one neuron where raster plots suggested that responses during movements were changing with repetition of trials, further two-way ANOVAs were carried out on each task separately with epoch and trial as main effects. Post hoc t-tests for multiple comparisons were carried out with the Waller-Duncan K-ratio T test, which compares type I and type II error rates based on Bayesian principles. These multiple range t-tests calculated the average neuronal activity in each epoch, ranked them in descending order and indicated groupings of epochs with and without statistical differences. A neuron was considered to be task selective if it showed one or more epochs that were significantly different between tasks. Cells showing modulations during the delay period (between ‘Ready’ and ‘Go’) were subjected to further statistical analysis by dividing the delay period epoch into two smaller epochs defined by the end of instruction.

Two composite sagittal maps based on a standard atlas (15) and showing the locations of all of the neurons tested were constructed for each patient group (PD and non-PD). Neurons were mapped onto the composite after correction of the stereotactic or anatomical map based on the identification of key physiological landmarks. For the patients undergoing thalamic surgery (non-PD), the location of each neuron was corrected with respect to the anterodorsal border of Vc as well as length of the track where cells responded to touch with a delimited receptive field and sites where microstimulation-evoked paraesthesias. For patients undergoing STN surgery for PD, the dorsal and ventral borders of STN and the dorsal border of the substantia nigra pars
reticulata (SNr) were used as landmarks to provide any necessary corrections to the location of each neuron, as reported previously (Hutchison, 1998). The mediolateral plane was not corrected based on physiological data, and was based on the initial target 10.5 mm or 12 mm lateral for STN and 14.5 mm lateral for thalamus from the midline co-ordinates of AC and PC from MR images.

RESULTS

Of the 52 neurons tested during the sequential button press task, 31 (60%) were task related. Of the task related neurons, 21 (68%) cells had similar responses in the MEM and FOL tasks (see Fig.2a). These cells were distributed amongst the various nuclei of the motor thalamus. The other 10 (32%) cells were considered to be task selective due to the fact that they either displayed modification of their activity during only one of the two tasks or they demonstrated a significantly larger response during one of the two tasks (see Fig.2b). The differences between tasks were seen during the delay period and phase-specific activity in 4 MEM selective and 7 FOL selective responses (one cell (Fig. 2c) had task specific components in both MEM and FOL tasks).

Seven of the task-related neurons in motor thalamus showed preparatory, delay period, or phase-specific changes in firing activity. Preparatory activity prior to movement onset was found in 2 cells, one of which was from a pain patient (Fig. 2a). In this case, the neurons responded during the FOL task with a gradual increase in activity until the Go signal, whereas in the MEM task there was a more abrupt increase in neuronal activity. In both tasks the 2s period prior to Go showed a significant increase in activity compared to the first 4s of the delay period (multiple range t-test A vs AA, p<
During the movement phase of the sequence, the responses were similar indicating that the cell was primarily concerned with motor or sensory aspects of the task.

Phase-specific activity describes a response restricted to a specific aspect or element of the movement sequence. Figure 2b shows an example of a neuron responding preferentially during the third button press of the MEM trial in a thalamic pain patient. There was a strong P3 increase in neuronal activity during MEM trials (ANOVA, d.f. = 1, 8, F=10.3, P<0.0001) which was absent during FOL trials. This neuron and the other MEM selective cells were all localized to the Voa area of the non-PD group. Another example of phase-specific activity is seen in FOL task in Fig2c. At the end of each button press there was a progressive decrease in activity relative to the background activity (see raster data Fig.2c), however, the decrease in activity at the end of P3 (end of trial) was significantly greater. This was immediately followed by a robust increase in activity (ANOVA, d.f.= 1, 8, F=14.25, P<0.0001) after the completion of the sequence, which was larger than the responses to each of the button presses. This neuron was localized to the Vop area and the other FOL selective neurons were distributed throughout the Voa, Vop, and Vim.

Delay period activity found in the epoch between Ready and Go was present during the MEM task for two of the cells; one of which is shown in Fig.2c. This neuron responded during the MEM task with a burst of increased activity in the delay period, which was absent during the FOL task. The burst occurred just after the onset of the third light (L3) 2.5s before Go. The neuronal activity following the increased activity burst until the Go signal was significantly higher than the activity during the initial 3s of the delay period (t-test, d.f. = 50, t = -7.95, p < 0.05). This neuron was localized to the Vop
area of thalamus of a chronic pain patient. Unlike the cited studies in monkeys, we did not observe selective responses to a particular sequence that would suggest a more direct role in sequential control, however we did find phase specific activity and likely with more testing of neurons and perhaps more training of the patients, a higher yield of these types of responses would be observed.

The distribution of responsive cells was relatively uniform between the patient groups with 20/33 (61%) cells responding to the task in the non-PD group and 11/19 (58%) cells responding in PD patients. Both PD and non-PD groups had similar numbers of cells showing responses with increases in activity (7;8) and decreases in activity (4;3), however PD patients lacked neurons with biphasic (increases and decreases in activity) (0;9) responses.

DISCUSSION

This study has shown that there are many different types of neuronal responses to a sequential reaching/button pressing task in the motor thalamus. The majority of the task-responsive neurons responded similarly to each of the three successive movements and to the two tasks. However, the responses of some neurons varied depending on the position of the movement within the sequence or on the type of task (i.e. FOL or MEM). Furthermore, some neurons also had preparatory or delay period responses.

Neurophysiological recordings in the monkey basal ganglia have shown selective responses of neurons for sequential movements under internal control rather than visual external control (Mushiake and Strick, 1995), (Hikosaka and Wurtz, 1983). In contrast, the cerebellum has been shown to be involved in movements under external control
(Jueptner et al., 1996; Mushiake and Strick, 1993). Our study examined the response to sequential button press in the human motor thalamus, which receives inputs from both the pallidum and the cerebellum. MEM selective neurons were found in the Voa, which is consistent with the anatomical evidence that pallidal output projects to the thalamic Voa area (Percheron et al., 1996) which in turn projects to the SMA, M1 and other premotor areas. The FOL selective neurons were found in many regions of the motor thalamus, i.e. the Vim, Vop, and Voa. While those found in Vim are consistent with anatomical evidence that the cerebellum projects to this thalamic region, the others suggest a wider distribution of such responses. Vim projects to the premotor cortex completing the purported neuronal loop involved in externally generated movements. Some evidence exists for functional specificity of neurons in pallido- and cerebellar-receiving areas of motor thalamus (van Donkelaar et al., 1999), suggesting specific subcircuits may also exist in humans and give rise to task-specific activity observed in this study for internally and externally generated movements.

The phasic burst of activity seen in the delay period of the MEM task is similar to that previously described in cortical neurons during a delayed matching-to-sample task (2). There is an increase in activation during memorization of the sequence to be subsequently performed. It is not likely that this response was related to visual cue information since there were no peaks of neuronal activity at the onset of the first two lights (ready, go). Another possibility is the consolidation of internal information on the third element, which may act as an “end” signal, reporting a completion of the sequence (Tanji, 2001). We noted that the PD group lacked neurons with MEM selective responses as well as neurons with biphasic responses which may reflect striatal dopamine
loss leading to dysfunction of a surround inhibitory system hypothesized as a mechanism of basal ganglia function (Mink, 1996).

Our observations provide support for the involvement of the thalamus in both internally and externally generated sequential movements. More than half of the neurons tested were task related and responded during the MEM and FOL tasks and in some cases the response patterns were task specific. Recordings in monkeys during an analogous button press task have found GPi and SMA neurons with similar activity to the thalamic neurons observed in this study (Mushiake and Strick, 1995; Tanji, 2001). Taken together with our results, this suggests that the basal ganglia-thalamo-cortical loop (and possibly also the cerbello-thalamic-cortical pathway) is involved in processing and organizing internally generated sequential movements. The thalamus also receives a large projection from cortex (Ilinsky et al., 1993), and thus we cannot rule out that corticothalamic input contributed directly to the responses observed.

In conclusion, this study has examined motor thalamic neurons on a task combining visual sensory, mnemonic and motor aspects and demonstrated complex responses including preparatory, delay period, phase-, and task-specific activity. These findings implicate the motor thalamus in both the planning and organization of sequential manual tasks in humans, a role heretofore ascribed to motor cortex and suggest that these responses are represented as a distributed network throughout the corticopalldidothalamic loop.

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FIGURE LEGENDS

**Fig. 1A.** Button press panel used for sequential reaching trials during the recordings of thalamic neurons. Light emitting diodes (LEDs) under each button indicated the button to be remembered and/or depressed (L1-L3). An LED in the middle of the panel served as the Ready/Go cue. The time line in part B below indicates the difference between the MEM and FOL tasks. **C** Reaction time (RT) was the time between onset of Go cue and onset of P1 and **D,** Movement time was from start of P1 to end of P3. No significant differences were seen between non PD group (hatched) and PD group (solid).

**Fig. 2.** Responses of thalamic neurons during MEM and FOL sequential reaching tasks. Each pair of averaged histograms shows the activity of a different thalamic neuron during the MEM and FOL tasks. Raster displays of the individual trials during each task are presented above the stimulus histograms (100ms bins). Histograms were created using Go, P1, P2, and P3 alignments to verify any temporal effects. The histograms shown in **a-c** are aligned on different event cues: **a, c:** Go; **b:** P3. **(a)** thalamic neuron responding during both MEM and FOL tasks. This cell also responded to passive movements of the shoulder and elbow **(b)** displays MEM- selective activity and this neuron also responded to passive shoulder manipulation and **(c)** displays MEM and FOL selective activity, cell responded to passive shoulder and elbow movements. The movement indicators for the neuron in part **c** are displayed in **(d).** The averaged accelerometer, EMG of wrist flexors (Fl.), and button tracings are aligned on the Go cue.

**Fig. 3.** Sagittal sections from the Schaltenbrand and Wahren stereotactic atlas at 12 mm **(a)** and 14.5mm **(b)** from the midline displaying the location of the neurons tested for the
sequential reaching task. Neurons tested in STN DBS surgery patients are shown in (a), and neurons tested during non-PD thalamic DBS surgery patients are shown in (b).

STN=subthalamic nucleus; RT=reticular thalamus; Voa=nucleus ventralis oralis anterior; Vop=nucleus ventralis oralis posterior; Vim=ventrointermedius; Vc=ventral caudal nucleus; AC=anterior commissure. The location of each neuron was corrected based on the physiological data such as the position of kinesthetic and tactile cells, and responses to electrical stimulation for each patient.
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