Tactile Discrimination Task Not Disturbed by Thalamic Stimulation

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**Key Words**
Touch · Stereotactic surgery · Thalamus stimulation · Parkinson disease

**Abstract**
The major pathway of human somatosensation passes through the ventrocaudal nucleus (Vc) of the thalamus. We tested the effect of direct electrical stimulation of the Vc on tactile discrimination in 5 Parkinson patients undergoing stereotactic thalamotomy. Raised gratings with lines 3, 4, or 6 mm apart were used. Patients had to actively touch test patterns placed in the hand contralateral to the thalamus under operation and compare it with a reference 3-mm grating held continuously in their other hand. Their performance was best for 6-mm, followed by 3-mm and then by 4-mm patterns regardless of electrical stimulation. Under Vc stimulation, patients recognized the 4-mm gratings slightly better. This can be explained either by the nature of thalamocortical interaction, which makes it resistant to external noise, or by the involvement of other pathways that circumvent the effect of thalamic stimulation.

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**Introduction**

The human thalamus is the major gateway of sensation to the cortex, and its dysfunction, e.g. in case of infarction, results in serious disabilities in the patient [1, 2]. Stereotactic neurosurgery provides a good opportunity to study thalamic function in a conscious patient. Ventrolateral and ventrointermediate thalamic nuclei are frequently targeted for treatment of movement disorders [3, 4]. The ventrocaudal nucleus (Vc), which is the major pathway of the somatosensory system from the periphery to the cortex, is located in the vicinity of the ventrointermediate nucleus and might be stimulated during the surgical procedure. One can expect that electrical stimulation would affect the relay of sensory signals through the thalamus and therefore would alter a patient’s sensory perception. Although electrical stimulation of the Vc frequently produces paresthesia or pain [3], it is not evident that a subject’s performance in tactile tasks is affected under electrical stimulation.

Previous studies on the role of the human thalamus in sensation have focused on very simple tests like median or tibial nerve electrical stimulation or finger vibration [5–13]. Yet, in another set of experiments, general behavioral and psychological performance of patients in whom the thalamus is somehow involved was investigated [14–18]. Here we selected an intermediate approach, using a cognitive task whose difficulty we could control.

The effect of direct electrical stimulation of the Vc core on the performance of human subjects in fine tactile discrimination is studied. Different areas in the Vc are devoted to different aspects of touch, the more anterior parts (core of Vc) being more engaged in fine touch [19]. The tactile stimuli were raised gratings with different spatial frequencies, which will be referred to hereafter as tactile frequency patterns (TFPs). One cannot use the whole three-dimensional configuration of stimuli and cannot rely on stereognosis, but rather has to depend on fine touch to discriminate such patterns. Individual performance in such patterns can be used to study the effect of electrical stimulation selectively on fine touch.

Given the resurgence of interest on modeling thalamic activity [20–24], such as, for example, the role of oscillations in thalamocortical interaction [21, 25], it is interesting to consider the effects of external noise in light of these recent views. An important question is at what level thalamic noise tolerance breaks down or why it does not at a given level. These issues will be raised in the discussion section where we explain the results of the experiment.
Patients and Methods

Subjects

Subjects were selected from Parkinson’s disease (PD) patients routinely admitted for stereotactic thalamotomy performed at the Shohada Hospital, Tehran. Subjects were informed about the experiment and all had given written permission for the experiment in addition to the operation prior to the surgery. The procedures and methods were in accordance with the guidelines set by the Research and Medical Ethics Committee at the Shohada Hospital/Shahid Beheshti University, which oversaw the experiment.

If a patient failed to respond satisfactorily to our tactile discrimination test during an evaluation session before surgery, due to either rigidity and tremor, or general cognitive and mood disorders, he or she was not enrolled in the study. Patients had no other neurological diseases except PD and had normal sensation, in that they had normal two-point discrimination.

Subjects were trained prior to surgery to perform the tactile discrimination task and were tested during the surgery. The experiment was carried out in patients in whom the electrode had crossed the Vc border (patients reported paresthesia). Patients in whom we failed to enter the Vc and to evoke paresthesia were excluded from the experiment.

Five PD patients, 4 males and 1 female, all right-handed, with a mean age of 48 years (range 39–62 years) satisfied the above criteria and were recruited for the experiment. Three patients underwent right and the other 2 left thalamotomy. The surgical procedure and the side of the thalamotomy were dictated by the patient’s history and physical examination and were not affected by his/her being selected as a subject for this experiment.
Patients could withdraw from the experiment if they felt tired or were not willing to cooperate during surgery, if constrained by medical conditions. None of the patients selected withdrew from the experiment.

**Materials**

Sensory stimuli (TFPs) were raised gratings made of a hard plastic material (fig. 2). There were three kinds of TFPs based on the distance between the grating lines (or spatial frequency), the lines being either 3, 4 or 6 mm apart in different TFPs. Each grating line was 0.2 mm wide, 18 mm long and 0.2 mm high. The whole stimulus was 10 cm long, mounted on a non-flexible piece of wood, which was 15 cm long, 2.3 cm wide and 3 mm thick. The subjects actively touched the stimuli with the tip of their index or thumb fingers.

**Surgical Procedure**

The patients were undergoing stereotactic thalamotomy for PD. The patients had to remain conscious to cooperate with the surgeon during the surgery. Vc is the gateway of sensory information from the body to somatosensory areas of the cortex. The hallmark of Vc stimulation is the sense of paresthesia in the contralateral limbs. The cells in the Vc are organized topographically in sensory homunculi for touch and pain, with cells responsive to fine touch arranged more anteriorly (in the core of the Vc) and those responsive to pain and temperature more posteriorly [3]. After physiological mapping and superimposing the obtained physiological map on the previously postulated anatomical map, if any trajectory passed through the proposed Vc coordinates, mentioned below, the patient was included in the experiment.
The Vc coordinates were postulated to be 3 mm anterior to the posterior commissure, 1 mm above the line joining the anterior commissure to the posterior commissure (AC-PC line) and 15 mm lateral to the midline.

The pulse was generated by a stimulator (Fischer, Medizin-Technik, Freiburg, Germany) capable of producing frequencies of 1, 2, 5, 10, 50, 100 Hz, pulse intensities from 0.1 to 24 V and pulse widths of 0.1–5 ms. In all patients, only pulse widths of 5 ms and a frequency of 50 Hz were used.

The voltage of stimulation was gradually increased until the patient had paresthesia. This confirmed the placement of the electrode in Vc. The voltage was then further increased to the level just short of the value that induced the sensation of pain, discomfort or myoclonus. This level (suprathreshold stimulation) was used in all trials in that patient. When the stimulation did not produce paresthesia at all or produced paresthesia in body parts other than in the tips of the index and thumb fingers of the desired hand, the patient was excluded from the experiment.

**Experimental Procedure**

One or 2 days before the operation, patients were trained for the tactile discrimination test. Patients were asked to keep one TFP (always the 3-mm TFP) in the hand ipsilateral to the side of the future operation. Then different TFPs were placed in their other hand and the subjects had to judge if the two test patterns in their hands were identical or not. Subjects were asked to actively touch TFPs with the index or thumb finger (same fingers in both hands). They repeated this task under supervision of one experimenter until they mastered the test.

In the operation room, patients were tested just before the surgery and retrained if necessary. The experiment started after the Vc was entered and good placement of the electrode was confirmed. Two (or in the case of patient ‘Ba’ three) alternative control (without electrical stimulation) and test (with electrical stimulation) blocks were taken. In each block, the reference tactile stimulus (always the 3-mm TFP) was held in the hand whose thalamus was not undergoing surgery (e.g. the left hand if the left thalamus was being operated on). One experimenter placed the test TFPs in random order in the hand whose contralateral thalamus was under surgery and the patient’s response, which was verbal, was recorded by another experimenter. The patient had to actively touch both TFPs and judge if the two TFPs were the same or different in 5 s. On the rare occasion that a patient failed to answer in this period, that trial was discarded. No trial was substituted for the omitted one.

The number of trials in test or control blocks varied in different patients. Patients’ hands were out of their visual field and they could rely only on active fine touch to discriminate between TFPs. Feedback about the correctness of responses was given to patients only during training, and were absent during the experiment.

**Results**

No patient had clinical signs of neuropathy or any deficit in tactile sensation, and two-point discrimination and stereognosis were normal. All demonstrated good cooperation in training sessions before the operation.
Table 1. The number of trials under test and control conditions in the different patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>No stimulation</th>
<th>Vc stimulation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Po.'</td>
<td>16 (7.41%)</td>
<td>32 (17.98%)</td>
<td>48</td>
</tr>
<tr>
<td>'No.'</td>
<td>50 (23.15%)</td>
<td>21 (11.80%)</td>
<td>71</td>
</tr>
<tr>
<td>'Sh.'</td>
<td>49 (22.69%)</td>
<td>23 (12.92%)</td>
<td>72</td>
</tr>
<tr>
<td>'Ak.'</td>
<td>49 (22.69%)</td>
<td>21 (11.80%)</td>
<td>70</td>
</tr>
<tr>
<td>'Ba.'</td>
<td>52 (24.07%)</td>
<td>81 (45.51%)</td>
<td>133</td>
</tr>
<tr>
<td>Total</td>
<td>216 (54.82%)</td>
<td>178 (45.18%)</td>
<td>394 (100%)</td>
</tr>
</tbody>
</table>

Vc stimulation induced paresthesia in all patients included in the experiment. Simple clinical tests, such as two-point discrimination and stereognosis, were tested during Vc stimulation and were identical to that in the non-stimulation condition. The voltage that induced paresthesia ranged from 4 to 8 V in different patients. Patients described paresthesia as a tingling sensation. The total numbers of trials that each patient fulfilled under Vc stimulation and non-stimulation conditions are presented in table 1.

Subjects could easily discriminate between the 6- and 3-mm TFPs, regardless of electrical stimulation (McNemar $\chi^2$ (A/D) = 53.157, d.f. = 1, p = 0.00000 and (B/C) = 42.875, d.f. = 1, p = 0.00000). There was no significant difference between control and test conditions (95.65 ± 2.47% correct ratio without stimulation vs. 92.98 ± 3.41% during stimulation, Yates $\chi^2$ 9.068, d.f. = 1, p = 0.79451). Discriminating 3- and 4-mm gratings from the reference TFP was more difficult. Subjects made errors in about one fifth of 3-mm TFPs (78.69 ± 5.4 correct ratio without stimulation vs. 78.57 ± 4.93 during stimulation, McNemar $\chi^2$ (A/D) = 24.721, d.f. = 1, p = 0.00000 and (B/C) = 16.254, d.f. = 1, p = 0.00006). In this case, there was no significant difference between control and test conditions either (Yates $\chi^2 = 0.033$, d.f. 1, p = 0.85632). For 4-mm grating, subjects had the maximum of errors (only 54.55 ± 5.7% correct without stimulation vs. 68.33 ± 6% during stimulation, McNemar $\chi^2$ (A/D) = 7.934, d.f. = 1, p = 0.00485 and (B/C) = 0.329, d.f. = 1, *p = 0.56628, also M-L $\chi^2 = 2.710$, d.f. = 1, p = 0.09974). Performance was even slightly better for stimulation blocks. but the difference between the two conditions did not reach significance (Yates $\chi^2 = 2.355$, d.f. = 1, p = 0.12478).

Overall, stimulation did not deteriorate discrimination (75.46% correct response without stimulation vs. 79.78% under stimulation, Yates $\chi^2 = 0.806,$
Table 2. The effect of Vc stimulation on discrimination of different tactile gratings

<table>
<thead>
<tr>
<th>TFP</th>
<th>Percent correct</th>
<th>SEM</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mm</td>
<td>78.3333</td>
<td>5.3634</td>
<td>60</td>
</tr>
<tr>
<td>3 mm</td>
<td>78.5714</td>
<td>4.9397</td>
<td>70</td>
</tr>
<tr>
<td>4 mm</td>
<td>68.8525</td>
<td>5.9786</td>
<td>61</td>
</tr>
<tr>
<td>4 mm</td>
<td>54.5455</td>
<td>5.7116</td>
<td>77</td>
</tr>
<tr>
<td>6 mm</td>
<td>92.9825</td>
<td>3.4135</td>
<td>57</td>
</tr>
<tr>
<td>6 mm</td>
<td>95.6522</td>
<td>2.473</td>
<td>69</td>
</tr>
<tr>
<td>Overall</td>
<td>77.4112</td>
<td>2.1094</td>
<td>394</td>
</tr>
</tbody>
</table>

SEM = Standard error of mean; n = number of trials. Overall patients’ performances are shown for different TFPs separately under stimulation and non-stimulation conditions.

d.f. = 1, p = 0.36936). There was no significant difference between different subjects (Pearson $\chi^2 = 2.476$, d.f. = 4, p = 0.64893). Results are summarized in table 2 and figure 1.

Discussion

The thalamus is a major gateway of sensory stimuli to the cortex. However, these results show that direct stimulation of the main somatosensory nucleus of the thalamus, the Vc, does not disturb a patient’s cognition of sensory stimuli for this test. Although this may sound nice from a clinical point of view, in the sense that deep brain stimulators do not affect a patient’s somatosensory ability, it raises questions about the mechanism of human sensation. First we have to argue for the adequacy and place of our electrical stimulation, and the appropriateness of the subjects and the tactile schema that we used.

The localization of the stimulating macroelectrode was on or above the AC-PC line, to preferably stimulate areas concerned with fine touch rather than crude touch, pain and temperature [3, 19]. The intensity of the thalamic stimulation was the highest level that did not produce pain or myoclonus in the projection field. The stimulation signal profile produced paresthesia in the fingers that performed the task. Rezai et al. [28] showed that the SI cortex is invariably activated when
the stimulation signal in the Vc is strong enough to produce paresthesia, so paresthesia seems to be a good indicator of the adequacy of the stimulating signal. Besides, the same signal profile in the ventrolateral nucleus of the thalamus was powerful enough to suppress tremor.

The results of this experiment can be generalized to discuss normal human sensation but with caution. PD patients might have cognitive deficits that make them use other strategies or pathways for performing the task [19, 30–32], and this may be the reason for their slower performance. However, they have a better preservation of microanatomy and physiology of sensory nuclei compared to pain disorder patients and especially central pain disorder patients [33, 34]. They are even used as a normal control group in studies on pain [33].

Unlike many other studies on the role of sensory nuclei of the thalamus in sensation, we did not use simple sensory stimuli like median nerve or finger electrical stimulation [5, 6, 8–11], but relied on more cognitive tasks to test the patients’ performance under thalamic stimulation. Moreover, the stimuli were designed so that the subjects could not use a three-dimensional shape and could not use stereognosis, but had to rely mostly on fine touch. Similar tasks were used in experiments on active touch in monkeys [26, 27].

Our research does not intend to provide direct evidence for or against probable recruiting of other pathways to circumvent the Vc to S1/S2 pathway during performance under stimulation, nor can it confirm if the patients are using other strategies to circumvent the effect of thalamic stimulation. Other brain areas are regarded to be important in active cognition of sensory stimuli (for example the posterior parietal cortex [5], cerebellum [6, 29] and basal ganglia [30]), but the nature of the task used in this experiment is a fine touch task, which is more dependent on an intact Vc to S1/S2 pathway. (Subjects recited their experience of a certain TFP under thalamic stimulation ‘to differ from a normal one but they somehow managed to correct the wrong feeling.’)

Therefore with seemingly good placement of the stimulating electrode, adequate signal intensity, and appropriate subject and task selection, the introduction of electrical noise in the main sensory nucleus of the thalamus did not deteriorate the patients’ performance, and even slightly enhanced performance when 4-mm stimuli were used. These findings do not accord with the classical concept regarding the thalamus as a relay station and electrical stimulation as a noise that interferes with this relay.

Our results seem to be in accordance with recent work studying S1 activation in case of infarction involving the thalamic sensory nucleus using PET [6]. Remy et al. [6] have shown that even a very simple tactile stimulus produces a normal activation in S1, even in case of Vc infarction. Another test of the sensory system, the two-point discrimination task, was also preserved in our study and was not affected by the thalamic stimulation.
Some hypotheses (models) of thalamocortical relation propose more complex functions for the thalamus than being just a relay station to the cortex [20–25]. In case of regarding an oscillatory relation between thalamus and cortex [21–23] or proposing that lower and higher areas can communicate to correct the effect of external noise [21], the thalamus might be resistant to the effect of external electrical stimulation, as might be the case in our experiment. This noise tolerance does not break down with conventional current profiles used in thalamotomy or deep brain stimulation.

We conclude that human somatosensation must be regarded as a complex process in which to explain the effects of intervention, which demand more accurate theories and models [31, 32].

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References