Chapter 1: Stereotactic neurosurgery for tremor

Abstract
A brief account is provided of developments that led to stereotactic thalamic surgery for tremor. The nomenclature of the ventrolateral thalamic nuclei and surgical targets are discussed, as well as some pathophysiological aspects. The results of thalamotomy for various kinds of tremor are described, along with the development of deep brain stimulation in the thalamus.

Historical notes
Stereotactic functional neurosurgery is founded on the work of Clarke and Horsley, who developed the first stereotactic instrument for application of intracerebellar animal experiments. Clarke tried in vain to convince his contemporary surgeons to apply this technique also for human brain surgery. In 1939 Meyers started his "experimental surgery" for parkinsonian patients and observed the superiority of the pallidotomy for the relief of tremor and other symptoms, but with a mortality rate of 15%, which findings were confirmed by others.

Spiegel and Wycis were the first to introduce stereotaxy as a surgical technique in humans for psychosurgery and the treatment of pharmacoresistant movement disorders. Several centers followed soon with their own stereotactic instruments. At first the globus pallidus and the ansa lenticularis were used as the surgical target structures, in accordance with Meyers, for the treatment of tremor and other parkinsonian symptoms. Because of disappointing long-term results of the pallidotomy for tremor, Hassler moved to the ventrolateral thalamus as the surgical target, based on his anatomical and physiological studies. He was supported by Cooper, who had inadvertently performed a thalamotomy instead of a pallidotomy with excellent tremor relief, and thereafter continued this procedure. Ever since, the ventrolateral thalamus has been the target structure of choice for the surgical arrest of tremor, as it still is today.

Nomenclature of the motor thalamus
Most neurosurgeons use the stereotactic atlas of Schaltenbrand and Wahren with its nomenclature of the thalamic nuclei according to Hassler. Hirai and Jones renamed the ventral thalamic nuclei, in accordance with the nomenclature used in experimental animal studies. They called the nucleus ventrooralis anterior (VoA) and posterior (Vop) of Hassler the ventral lateral anterior nucleus (VLA), which receives pallidal efferents. The nucleus ventrointermedius (Vim) of Hassler was called the ventral lateral posterior nucleus (VLP) in their nomenclature, and this is the relay nucleus for cerebellar efferents. The nucleus ventrocaudalis (Ve) of Hassler was renamed as the ventral posterior lateral and medial nucleus (VPL,m) receiving lemniscal input.

Surgical target in the thalamus
Originally, the anterior part of the ventrolateral nuclei (VoA and Vop) was the surgical target. The introduction of microrecordings during surgery indicated that the posteriorly situated Vim was a more suitable target for tremor surgery. Using this technique Ohye demonstrated that small lesions in Vim could suppress tremor permanently, whereas a more anterior lesion in Vop had more effect on rigidity in parkinsonism. Favourable effects of lesions on tremor were demonstrated in the subthalamic area, a procedure also called campotomy. However, nowadays Vim is the target of choice for tremor surgery in the thalamus for most surgeons.
**Pathophysiological considerations**

Thalamic surgery is effective for tremor suppression in a variety of disorders, suggesting a common final pathway in the pathophysiology of these different types of tremor.

In Parkinson's disease, the key pathological change is degeneration of dopaminergic cells in the substantia nigra, resulting in dopamine depletion of the basal ganglia. Oscillating activity in the basal ganglia-thalamo-cortical loop arises, that might be due to synchronization of rhythmic activity in various basal ganglia connections, which under normal conditions are separated by dopaminergic input. This abnormal activity is hypothesized to cause the tremor. Additionally, oscillating activity in the cerebello-thalamo-cortical circuit is also present, which is thought to modulate the frequency of the tremor, and is probably involved in the suppression of resting tremor during voluntary movements.

Essential tremor is a mostly hereditary condition in which no morphological changes have been identified, suggesting a functional abnormality within the central nervous system. The pathophysiological mechanism is unclear so far, but abnormal oscillating activity is present in the olivocerebellar circuit, which might be transmitted to the motor cortex via the cerebello-thalamo-cortical connections.

Cerebellar intention tremor, as occurs in multiple sclerosis, is also poorly understood. A major factor in the generation of the tremor is probably disturbed timing and grading of the activity of antagonistic muscles. Both somatosensory feedback through cortico-cerebellar connections, and cerebellar feed-forward through cerebello-thalamo-cortical projections are thought to be involved in the generation of the tremor.

There are many uncertainties and alternative hypotheses for the pathophysiology of the various types of tremor discussed, but all share a role of oscillatory activity that runs through the thalamus. Presumably this abnormal oscillation is halted or diminished by stereotactic thalamic surgery, explaining the suppression of tremor, irrespective of its cause.

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**Thalamotomy for tremor**

The most common types of tremor accessible for stereotactic neurosurgery are listed in table 1. The surgical results for the various types of tremor are discussed.

**Table 1 Clinical types of tremor for which thalamotomy has been applied.**

<table>
<thead>
<tr>
<th>Type of Tremor</th>
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<tbody>
<tr>
<td>Resting tremor</td>
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<tr>
<td>Parkinson's disease</td>
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<tr>
<td>Action tremor</td>
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<tr>
<td>essential tremor</td>
</tr>
<tr>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>posttraumatic</td>
</tr>
<tr>
<td>posthemiplegic</td>
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<tr>
<td>associated with neuropathy</td>
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<tr>
<td>writing tremor</td>
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**Parkinson's disease**

In 1969 at the third symposium on Parkinson's disease in Edinburgh, after more than 37,000 stereotactic interventions, there was general agreement about an improvement of the tremor in 80% to 90% of the patients, with a functional improvement in 30% to 50%. Bilateral thalamotomy was considered hazardous because of a higher incidence of adverse events. Long-term follow up studies later confirmed a permanent improvement in ~80% of the cases. The introduction of levodopa temporarily reduced the number of thalamotomies dramatically. However, from the 1980s there was a revival of functional stereotactic interventions because of shortcomings of the pharmacotherapy.

Studies from operations performed after 1970 showed that unilateral thalamotomy improved the contralateral tremor permanently in ~90% of the patients, and recurrence of the tremor of ~15% mostly appeared in the first three postoperative months. The levodopa-induced dyskinesias were either relieved or prevented in the contralateral extremities in a high percentage. The morbidity was reported between 9% and 23%. These figures are higher than those of the pre-levodopa era. Reasons for this are probably more precise registration.
and postponement of surgery to a later stage of the disease because of levodopa therapy.27

**Essential tremor**

Although essential tremor is far more common than Parkinson's disease, the number of patients referred for surgery is small. Only five studies could be traced with more than 10 patients. Long term results demonstrated a permanent satisfying tremor relief in the contralateral extremities of 69% to 93%.30-34 In the analysis of van Manen,34 only 30% of the patients were completely satisfied with the result despite a permanent tremor relief for 90%. The morbidity of thalamotomy in essential tremor is similar to that in Parkinson's disease.

**Action tremor caused by multiple sclerosis**

Haddow et al.35 reviewed 14 articles concerning thalamotomy in multiple sclerosis patients with tremor published between 1960 and 1992. The total number of patients amounted to 234, including 10 of their own. There was a satisfying short term improvement of the tremor in more than 75% of the patients and long term benefit between 50% and 73%.36-38 The functional outcome was mainly determined by accompanying symptoms, such as limb and truncal ataxia, speech disorders, and paresis, and was rather disappointing in the long term with sustained improvement of 25-47%.35-38 The morbidity was high, with percentages between 27% and 78% for transient adverse events and between 16% and 41% for permanent complications.36,38,39 One patient has been reported with a relapse of the multiple sclerosis, possibly in relation to the surgery.36

**Posttraumatic tremor**

Posttraumatic tremor was observed in 19% of patients in a series of 221 survivors of severe head-injury, which disappeared within one year in 10% of the patients.40 The remaining 9% of patients had a persistent kinesogenic tremor, which became manifest between 2 weeks and 6 months after the incident. Three types of posttraumatic syndromes related to tremor can be discerned: (a) posttraumatic cerebellar syndrome characterized by bilateral occurrence of kinesogenic tremor and cerebellar deficits; (b) posttraumatic "midbrain syndrome": a combination of mostly unilateral kinesogenic tremor, and contralateral weakness and pyramidal findings; and (c) pure intention tremor, mostly in children.41 Pharmacotherapy is generally not effective.

Thalamotomy was reported to have a favourable effect on the tremor, symptomatically as well as functionally.42-44 Lasting improvement of the tremor in more than 80% is reported.44 Careful selection of patients for surgery is important. Ataxia, dysarthria, and pseudobulbar palsy are relative contraindications.42 Thalamotomy for the "posttraumatic cerebellar syndrome" may expose a cerebellar deficit after relief of the tremor, which can have a negative impact on the outcome of surgery. Thalamotomy for tremor in the posttraumatic midbrain syndrome may cause a deterioration of other symptoms (dysarthria, swallowing disturbance, or hemiparesis). As a rule, surgery must not be performed before one year after the manifestation of the tremor because of the possibility of its spontaneous remission. The decision to operate demands a careful weighing of the disability due to the tremor, the impact of other posttraumatic deficits, the risk of adverse events by surgery, and the expectations of the patient of the outcome of surgery.

**Other types of action tremor**

Posthemiplegic tremor becomes manifest after a delay of days to months after the stroke and is described as intention and postural tremor, often with involvement of proximal muscles. Little is known about the effects of thalamotomy.46 Ohye et al. remarked that the posthemiplegic tremor cases were the most difficult group to treat and that the surgical lesions were much larger than those for other tremor types.45,46 In most patients, lasting tremor relief could be achieved with improvement of functioning and relatively few persistent surgical adverse events, such as dysarthria, ataxia, and paresis.36,39,45-47 Of importance for the outcome was that the Vim remained intact.46
Tremor in peripheral neuropathy is often observed in chronic sensory motor neuropathy of different etiologies. Mostly there is a postural and intention tremor, resembling essential tremor. Generally, if the neuropathy responds to treatment, then the tremor also improves. However, in untreatable cases, the remaining tremor may be quite disabling. Remarkably only one study could be found describing treatment by thalamotomy.

Writing tremor, a task-specific tremor, can be very disabling. Satisfying symptomatic and functional results of thalamotomy were described in three patients.

**Thalamic stimulation**

During stereotactic functional neurosurgical procedures, electrical stimulation is used to determine the optimal position for placement of the lesion, and to check if side-effects occur attributable to nearby anatomic structures such as the internal capsule. As the effects of lesioning can be simulated and predicted by electrical stimulation, implanting a permanent electrode for continuous stimulation rather than lesioning was a logical technical development in order to reduce side-effects of surgery, and to make the procedure reversible in case of disappointing symptomatic and functional improvement.

The first description of implantation of permanent electrodes in the thalamus dates back to 1974, with pain as target symptom. Thalamic stimulation for tremor suppression was first attempted for severe bilateral intention tremor due to multiple sclerosis. In 1991 Benabid et al. published a landmark paper describing results of long term thalamic stimulation for tremor in Parkinson's disease and essential tremor. The improvement of tremor seemed to be similar to that after thalamotomy, and morbidity appeared less after stimulation.

More long term follow-up data and the outcome of a comparative study of thalamic stimulation versus thalamotomy were necessary, to determine the role of thalamic stimulation in the surgical treatment of tremor of various etiologies.

**References**


