Human mediodorsal thalamic nucleus as a potential target for deep brain stimulation: review of the literature and anatomical considerations

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Abstract

Introduction

The dorsomedial or mediodorsal thalamic nucleus is embedded in different basal ganglia-thalamocortical loops, which integrate cognitive and emotional aspects of human behaviour. It is involved in several neuropsychiatric conditions. Mediodorsal thalamic nucleus deep brain stimulation has been repeatedly reported in animal models. The purpose of this article was to review critically the literature regarding basic science and clinical data of the mediodorsal thalamic nucleus, considering it as a potential deep brain stimulation target.

Discussion

The mediodorsal thalamic nucleus is an association hub mediating interconnections mainly with the prefrontal cortex. It has strong reciprocal connections with the dorsolateral prefrontal cortex, suggesting that it participates in higher cognitive functions such as spatial working memory. Specifically, schizophrenia is associated with volume and neuronal changes in the mediodorsal thalamic nucleus and pulvinar. In the mediodorsal thalamic nucleus of schizophrenic subjects, neuronal number is significantly lower and neuronal size is significantly smaller. The mediodorsal thalamic nucleus also plays the main role in amygdalo-hippocampal seizures and controls the limbic seizures. Experimental data showed that electrical stimulation of the mediodorsal thalamic nucleus elicits field potentials in several cortical areas of the frontal lobe. From an anatomical point of view, an electrode trajectory to the human mediodorsal thalamic nucleus is achievable without traumatizing cortical vessels, the lateral ventricles or basal ganglia nuclei.

Conclusion

Treatment-resistant schizophrenia could theoretically be the most probable indication for such a minimally invasive intervention.

Introduction

The dorsomedial or mediodorsal thalamic nucleus (MDTN) has extensive and reciprocal connections with the prefrontal cortex and limbic structures including limbic cortex, hippocampus and basolateral amygdale. The MDTN participates in cognitive and emotional processes. Deep brain stimulation (DBS) applied to MDTN has been repeatedly reported in animal models, but, to the writer’s knowledge, not yet in humans. Considering the worldwide acceptance and progress of DBS surgery, it is probably just a matter of time for such a minimally invasive procedure to be applied to the human MDTN. Regardless of the indication and time of such an application, its safety always comes first. The primary purpose of this article was to review critically the literature regarding basic science and clinical data of the MDTN, considering it as a potential target for DBS.

Methods

The existing literature regarding anatomical, functional and clinical data of the MDTN, as well as experimental data of MDTN stimulation, was reviewed. Comments on the stereotactic neurosurgical anatomy of the human MDTN DBS, with great respect to the safety of such a procedure, are also provided.

Discussion

Anatomical and functional data

The MDTN is the second largest nucleus aggregation located within the medial part of the thalamus and is closely related to the centromedian/parafascicular nucleus complex. Distinct thalamic nuclei, like the MDTN and centromedian/parafascicular complex, are embedded in different basal ganglia-thalamocortical loops, which integrate cognitive and emotional aspects of human behaviour.

The human MDTN is in a crucial position that allows it to establish connections with diverse cerebral structures. It is an association hub mediating interconnections mainly with the prefrontal cortex. In primates and in vivo diffusion tensor tractography findings in both humans and monkeys confirm its role in relaying networks that connect to the dorsolateral prefrontal, orbitofrontal, frontal medial and cingulate cortices.

The MDTN has strong reciprocal connections with the dorsolateral prefrontal cortex, suggesting that the MDTN, like the dorsolateral prefrontal cortex, participates in higher cognitive functions such as spatial...
working memory. However, the manner in which these two structures participate in these processes differs in that the MDTN participates more in motor control aspects compared with the dorsolateral prefrontal cortex. Additionally, more MDTN neurons participate in prospective information processing than dorsolateral prefrontal cortex neurons do. Interestingly, the MDTN has been found to present maximal functional connectivity with the dorsolateral prefrontal cortex during focusing-of-attention tasks.

The parvocellular sector of the MDTN is involved in memory recall. The functional specialisation of the parvocellular MDTN accords with its connectivity to the dorsolateral prefrontal cortex, highlighting the role of this thalamocortical network in explicit memory. The magnocellular sector of the MDTN, in monkeys, is required for new learning of scene discriminations but not for their retention and retrieval.

Furthermore, bilateral MDTNs and ventrolateral thalamic nuclei have remarkably similar connectivity maps and resemble those of the whole thalamus, suggesting their crucial contributions to the thalamic–visual correlations. Given that the MDTN is connected to limbic cortical regions, it is not surprising that thalamic activation in the bilateral MDTN has been reported during erotic and emotional picture perception at (X, Y, Z) = (7, −13, 10) coordinates in Talairach space. Furthermore, this nucleus is also involved in penile erection.

Clinical data
The importance of neuronal interactions in development, the cortical dependence of many thalamic nuclei and the phenomenon of trans-synaptic degeneration suggest possible abnormalities in thalamic nuclei with connections to other brain regions implicated in schizophrenia. Because frontal and temporal lobe volumes are diminished in schizophrenia, volume loss could characterise their primary thalamic relay nuclei (MDTN and pulvinar). Specifically, schizophrenia is associated with volume and neuronal changes in the MDTN and pulvinar, the major association nuclei of the thalamus. Volumes of the MDTN and pulvinar nuclei are smaller in patients with schizophrenia. Women seem to have larger MDTN relative volumes than men among controls, but men seem to have larger volumes than women among schizophrenic patients. Other authors reported that schizophrenia is associated with a moderate volume reduction in the left MDTN. When expressed as percentage of total brain volume, pulvinar and MDTN together are also reduced in schizotypal personality disorder. Reductions seem to be more prominent in the left hemisphere.

Several studies have also pointed to alterations in neuron densities and total neuron numbers of the MDTN in schizophrenia. Specifically, in the MDTN of schizophrenic subjects, neuronal number is significantly lower and neuronal size is significantly smaller. Chronic schizophrenic patients have a 40–50% reduction in the total number of nerve and glia cells of the MDTN and nucleus accumbens compared with controls. Interestingly, the total number of nerve cells in the MDTN is significantly reduced in leucotomised schizophrenics compared with chronic schizophrenics.

While therapeutically induced and circumscribed lesions of the MDTN rarely result in long-lasting memory deficits, pathological processes in MDTN are more likely to be followed by severe memory disturbances if one or more particular structures in addition to MDTN are included in the lesioned regions. Specifically, damage to the magnocellular sector of the human MDTN is associated with both retrograde and anterograde amnesia.

Acute isolated disorientation of time, chronotaraxis, is an uncommon manifestation of thalamic stroke. Acute thalamic chronotaraxis is a specific clinical picture that accurately predicts a small artery disease of the thalamus involving the MDTN. This clinical syndrome appears to have a good clinical recovery.

Finally, the MDTN plays the main role in amygdalo-hippocampal seizures and controls the limbic seizures. Therefore, a therapeutic approach to the MDTN seems to be clinically very important.

Experimental data regarding mediiodorsal thalamic nucleus stimulation
Cumulative studies suggest that the MDTN is involved in limbic seizure activity. Wang et al. aimed to investigate whether MDTN DBS can protect against seizures induced by amygdaloïd kindling in rats. They studied the effect of low-frequency (1 Hz) or high-frequency (100 Hz) stimulation in the MDTN on amygdaloïd kindling seizures. Their results suggested that MDTN DBS might have no significant effect on limbic seizures.

Tanibuchi applied electrophysiological and anatomical studies on MDTN projections onto the prefrontal cortex in cats. Electrical stimulation of the MDTN elicited field potentials in the gyrus proreus, frontalis, rectus and cinguli anterior of the ipsilateral prefrontal and adjacent cortical areas. The results of a laminar field potential analysis indicated that the field potentials could be regarded as a combination of deep and superficial thalamocortical responses. By injecting horseradish peroxidase into the MDTN, horseradish peroxidase-labelled terminals were distributed in the prefrontal and adjacent cortical areas where the field potentials were elicited. Densely labelled terminals in cortical layer I were distributed where the association and thalamocortical responses were prominent, while those in layers III–V were distributed.

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in the areas where the deep thalamocortical responses were prominent.\(^2\)

Ewing et al.\(^2\) explored the regions activated by MDTN DBS through examination of immediate early genes as markers of neuronal activation in rats. Stimulation was delivered unilaterally with constant current 100 μs duration pulses at a frequency of 130 Hz delivered at an amplitude of 200 μA for 3 h. Brains were removed, sectioned and radio-labelled for the genes zif-268 and c-fos. In anaesthetised rats, MDTN DBS produced robust increases in the expression of zif-268 but not c-fos localised to regions that are reciprocally connected with the MDTN, including the prelimbic and orbitofrontal cortices, as well as premotor cortex, indicating an increase in synaptic activity in these regions. These findings map those brain regions that are persistently activated by high-frequency electrical stimulation of the MDTN by a putatively antidromic mechanism, which may be relevant to neuropsychiatric disorders such as schizophrenia, in which thalamocortical systems are disrupted and DBS protocols are being considered.\(^2\)

Rinaldi et al.\(^25\) recorded electrical activity from single cells in the thalamus of 10 patients with chronic pain associated with deafferentation. Under local anaesthesia, these patients underwent either electrode implantation or thalamotomy for treatment of their pain. In 8 of the 10 patients, single units were identified as discharging spontaneously in high-frequency, often rhythmic, bursts. The discharges were of two types: short bursts comprised 2–6 spikes with a burst frequency of 1–4 per sec and long trains of 30–80 spikes of similar frequency. Reconstruction of electrode trajectories indicated that recordings were made from the region corresponding to the lateral aspect of the MDTN, the central lateral nucleus, a small part of the central median nucleus and the parafascicular nucleus. In the eight patients in whom spontaneous neuronal burst activity was exhibited, it was impossible to study activity evoked by natural cutaneous stimulation due to the continuous spontaneous neuronal discharges. Their findings suggested that spontaneous neuronal discharge in patients with pain related to deafferentation...
is more widespread in the central nervous system than it had been previously appreciated.

Akopyan et al. studied the effects of the associated MDTN spike activity of respiratory neurons in the medulla oblongata and on respiration in normal conditions and in oxygen insufficiency. At normal atmospheric pressure, electrical stimulation of the MDTN had predominantly inhibitory effects. At the initial phase of hypoxia, at a 'height' of 4000–5000 m, hypoxic activation of neuron discharge frequency occurred, with an increase in the frequency of respiration. In these conditions, the inhibitory effect of stimulation of the MDTN was less marked than in normoxic conditions. The opposite effect occurred at the second phase of hypoxia (7500–8000 m)—inhibition of activity in the medulla oblongata and thalamic centre. In severe hypoxia, there was inhibition of neuron spike activity and a decrease in the frequency of respiration, which became superficial; in these conditions, the inhibitory effect of the thalamus was insignificant

Based on the above literature data, the clinical conditions where the MDTN is involved are summarised in Table 1.

### Table 1 Clinical conditions where the MDTN is involved

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Schizotypal personality disorder</td>
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<td>Memory disturbances (retrograde amnesia, anterograde amnesia)</td>
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<tr>
<td>Chronotaraxis</td>
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<tr>
<td>Epilepsy (amygdalo-hippocampal seizures, limbic seizures)</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Respiratory response to hypoxia</td>
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<td>MDTN, mediodorsal thalamic nucleus; chronotaraxis, acute isolated disorientation of time.</td>
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Human mediodorsal thalamic nucleus deep brain stimulation: anatomical considerations

The white matter fibres location, mainly the internal capsule and corona radiata, usually provides a respective width of the trajectory angle, where the electrode could safely pass. An electrode trajectory to the human MDTN is achievable without traumatising cortical vessels, the lateral ventricles or basal ganglia nuclei (caudate nucleus and putamen). The safest angle of such a trajectory is that which minimises the chances of traumatising grey matter structures (nuclei, cortex) as well as cerebral vessels and ventricles.

To the author’s anatomical experience, stereotactic coordinates $(X, Y, Z) = (7, -13, 10)$ (MDTN activation during erotic and emotional picture perception) offer a target point within the MDTN limits in approximately 90% of cases (with the rest being located either at the cingulate gyrus or within the lateral ventricle). Regarding the anatomical parameters of the safest trajectory to the MDTN (at the above-mentioned coordinates), its coronal angle is variable (12–80°, mean: 56°), as is also its coronal projection's length (36–63 mm, mean 49 mm) (Figure 1), with no significant difference between right and left hemispheres.

Conclusion

The MDTN is embedded in different basal ganglia-thalamocortical loops, which integrate cognitive and emotional aspects of human behaviour. It is an association hub mediating interconnections mainly with the prefrontal cortex. It has strong reciprocal connections with the dorsolateral prefrontal cortex, suggesting that it participates in higher cognitive functions such as spatial working memory. In the MDTN of schizophrenic subjects, neuronal number is significantly lower and neuronal size is significantly smaller. MDTN DBS has been repeatedly reported in animal models. Experimental data showed that electrical stimulation of the MDTN elicits field potentials in several cortical (limbic) areas of the frontal lobe. From an anatomical point of view, an electrode trajectory to the human MDTN is achievable without traumatising cortical vessels, the lateral ventricles or basal ganglia nuclei. Treatment-resistant schizophrenia could theoretically be the most probable indication for such a minimally invasive intervention.

Abbreviations list

DBS, deep brain stimulation; MDTN, mediodorsal thalamic nucleus.

References

6. Jakab A, Blanc R, Berényi EL. Mapping changes of in vivo connectivity patterns...


