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The role of the thalamus in the human subcortical vestibular system

Vestibular pathways of the human brainstem to the thalamic nuclei and their functional relevance: Evidence from human lesion- and functional imaging studies

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Abstract. Most of our knowledge concerning central vestibular pathways is derived from animal studies while evidence of the functional importance and localization of these pathways in humans is less well defined. The termination of these pathways at the thalamic level in humans is even less known. In this review we summarize the findings concerning the central subcortical vestibular pathways in humans and the role of these structures in the central vestibular system with regard to anatomical localization and function. Also, we review the role of the thalamus in the pathogenesis of higher order sensory deficits such as spatial neglect, pusher syndrome or thalamic astasia and the correlation of these phenomena with findings of a vestibular tone imbalance at the thalamic level.
By highlighting thalamic structures involved in vestibular signal processing and relating the different nomenclatures we hope to provide a base for future studies on thalamic sensory signal processing.

Keywords: Medial longitudinal fascicle, ascending tract of Deiters, brachium conjunctivum, ipsilateral vestibulothalamic tract, crossed ventral tegmental tract, vestibular, thalamus, neglect, pusher, astasia

Glossary

ATD	Ascending tract of Deiters
BC	Brachium conjunctivum
BOLD	Blood oxygen level dependent
CVTT	Crossed ventral tegmental tract
DBS	Deep brain stimulation
FDG-PET	Fluordesoxyglucose-Positron-Emission-Tomography
IFG	Inferior frontal gyrus
INC	Interstitial nucleus of Cajal
INO	Internuclear ophthalmoplegia
IPL	Inferior parietal lobule
IVTT	Ipsilateral vestibulothalamic tract
ML	Medial lemniscus
MLF	Medial longitudinal fascicle
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
MVN	Medial vestibular nucleus
OTR	Ocular tilt reaction
oVemp	Ocular vestibular evoked myogenic potentials
PCA	Posterior cerebral artery
rCBF	regional cerebral blood flow
rCGM	regional cerebral glucose metabolism
riMLF	Rostral interstitial nucleus of the medial longitudinal fascicle
SCC	Semicircular canal
SCP	Superior cerebellar peduncle
SHV	Subjective haptic vertical
SLF	Superior longitudinal fascicle
SPV	Subjective postural vertical

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SVN Superior vestibular nucleus
SVV Subjective visual vertical
VLBM Voxel based lesion behavior mapping
VN Vestibular nerve
For abbreviations of the thalamic nuclei see Fig. 2

1. Introduction

The role of the thalamus in central vestibular processing and the target structures of vestibulothalamic connections are poorly understood in humans. Thus, we would like to present an overview of human lesion- and functional imaging studies concerning central vestibular processing in the brainstem and specific thalamic "vestibular" nuclei and point out implications for future research.

Most of our knowledge regarding vestibular processing in the brainstem and thalamus is derived from animal studies in different species. Based on these studies otolith and semicircular canal (SCC) signals are transferred from the inner ear hair cells to the vestibular nuclei and enter the medullary brainstem together with the cochlear and facial nerves. Saccular and posterior SCC signals are transmitted via the inferior branch of the vestibular nerve (VN), and signals from the utricle, the anterior and horizontal SCC pass by the superior branch of the VN. Usually otolith signal encoding neurons have a sensitivity to both angular acceleration and tilt (i.e. semicircular canal and otolith signals) [22] and signals converge in the vestibular nuclei [2]. The nerve fibers divide in an ascending branch to the superior vestibular nucleus [15] (SVN) and a descending branch to the medial and inferior vestibular nuclei. The different vestibular nuclei are heavily interconnected. Output of the vestibular nuclei reaches cervical, cerebellar, ocular-motor and eye-head coordination centers or higher order sensory integration structures (for review see Büttner-Ennever et al. [15]). The main sources of output are the magnocellular regions of the medial and superior vestibular nucleus and adjacent dorsal Y group.

There are several ascending vestibular pathways that have been described in animal studies whereas studies on human vestibulothalamic processing are scarce [36]. Only a few lesion and functional imaging studies concerning this matter are available. While most lesion studies are descriptive in nature, analysis of functional imaging data in most cases is limited to the poor spatial resolution of the blood oxygen level dependent (BOLD-)/regional cerebral glucose metabolism (rCGM) signal and thus correlation of activation/deactivation patterns with anatomical structures in the brainstem and thalamus lacks statistical power. Furthermore, functional imaging studies reveal all areas that are activated during a task relative to a certain baseline (i.e. correlation) but do not reveal areas that are necessary for a task (i.e. causality) [41,45].

2. Ascending pathways

Five pathways carrying otolith and/or semicircular canal signals have been described in animal studies [44,53]. The medial longitudinal fascicle (MLF), the ascending tract of Deiters (ATD), the crossed ventral tegmental tract (CVTT), the brachium conjunctivum (BC; superior cerebellar peduncle, SCP) and the ipsilateral vestibulothalamic tract (IVTT). For review see Zwergal, A. and co-workers [53] and Pierrot-Deseilligny and colleauges [44].

As mentioned above most functional imaging studies focus on cortical vestibular processing due to the lack of high resolution of functional MRI in the brainstem. That means that functional imaging which provides information of functionally connected brain areas (i.e. tracts) unfortunately cannot be applied to differentiate the brainstem tracts involved in vestibular signal processing. In functional imaging it has been shown that the thalamus is an integral part of vestibular processing but again the exact anatomic location of the nuclei involved cannot be investigated with this method. Thus, most information on the brainstem pathways in humans to date stems from clinical observations and lesion studies.

2.1. Medial longitudinal fascicle (MLF) in humans

The medial longitudinal fascicle is a bilaterally developed pathway that interconnects the ocular motor nuclei and is well known to transmit vestibular information from the vestibular nuclei (mainly MVN and SVN) to ocular motor nuclei and the midbrain integration centers (INC, riMLF) to provide eye-head coordination in roll. In a descriptive lesion study Brandt and Dieterich [14] found that lesions of the caudal part of the MLF and the VN lead to ipsiversive ocular tilt reaction (i.e., head tilt, ocular torsion, skew deviation and deviation of the subjective visual vertical (SVV); ipsilateral eye undermost), while lesions of the rostral pons and midbrain (at the site of the oculomotor nuclei, the riMLF and the interstitial nucleus of Cajal (INC)) lead

to contraversive OTR. Their hypothesis was that this graviceptive pathway is the MLF whose fibers cross in the pontomedullary brainstem. In 36% of their cases, patients exhibited internuclear ophthalmoplegia (INO) in addition to OTR supporting their hypothesis [14]. In 2008 Zwergal and co-workers examined 120 patients with hemorrhagic or ischemic brainstem stroke [52]. They found that 98% of the patients with INO due to brainstem stroke also had at least one component of contraversive OTR, mostly deviation of SVV but also skew deviation and ocular torsion in more than 50% of the cases. They also observed OTR in patients with "one-and-a-half-syndrome". Therefore they figured that vestibular (mainly otolith) fibers must be included in or adjacent to the MLF. It is noteworthy that this assumption stems from the clinical picture and inspection of MRI scans, neither descriptive lesion mapping nor statistical analyses were carried out [52]. The fact that INO is a sign of MLF lesions has been statistically confirmed by Baier and co-workers using voxel-based lesion behavior mapping (VLBM) [5]. Through VLBM it is possible to correlate brain damage with behavior voxel-by-voxel [9] and to find a statistical association of damaged voxels and impaired function [45].

Oh and colleagues [42] provided more evidence of the MLF carrying otolith signals by combining the results of ocular vestibular evoked potential (oVemp) testing to air conducted sound with VLBM. They found regions associated with pathological oVemps mainly to be located in the dorsomedial tegmentum of the pons and midbrain corresponding to the MLF and oculomotor nuclei. Furthermore, there was evidence of voxels being frequently damaged in patients with pathological oVemps that project to the Crossed Ventral Tegmental Tract (CVTT) [42].

In summary, even though there have been multiple studies on the role of the MLF in brainstem vestibular processing, none of the studies have focused so far on a possible ascending branch of the MLF to the thalamus. In animal studies there is evidence of some MLF fibers terminating in the thalamus; the distinct nuclei in which MLF fibers end have not been investigated in humans so far.

2.2. Ascending tract of Deiters (ATD) in humans

To our knowledge no reports on human vestibular processing via the ascending tract of Deiters to the thalamus have been published until now. In cats [37] this tract connected the medial vestibular nucleus and the nucleus prepositus hypoglossi with the III. cranial nerve nucleus, the Centre Médian (Ce/CM) nucleus and the Ventrolateral nuclear complex (Vim, Voi/VL) (see Table 1 below for the different nomenclatures of thalamic nuclei) of the ipsilateral thalamus. The reason why the contribution of ATD lesions has not been appreciated to contribute to vestibular dysfunction in humans might be due to its close proximity to the MLF which makes differentiation difficult.

2.3. Crossed ventral tegmental tract (CVTT) in humans

Evidence of vestibular signals in human CVTT is rare and restricted to case reports and assumptions but no systematic clinical studies have been carried out. Kim and colleagues [33] published a case report in which they described a patient with dorsal pontine infarction presenting with perverted head shaking nystagmus (downbeat nystagmus after viguorous head shaking in the horizontal plane) which they attributed to a lesion of the crossed ventral tegmental tract. Oh and co-workers [42] demonstrated with VLBM that pathological oVemps are associated with lesions of the CVTT even though it is not clear whether the voxels most commonly injured are located in the MLF or the CVTT. These clinical findings support those from animal studies that dorsal Y-group neurons transmit upward smooth pursuit signals via the CVTT (and the BC) [44]. Again, the exact termination of this tract in the thalamus remains unclear.

2.4. Brachium conjunctivum (BC)/superior cerebellar peduncle (SCP) in humans

Baier and co-workers [6] conducted a study of signs of ocular tilt reaction in 79 patients with unilateral brainstem lesions. In addition to other findings significant voxels associated with contraversive ocular and SVV tilt were found in the brachium conjunctivum (BC) (also affected: riMLF, INC, MLF). Affection of verticality perception in cerebellar lesions had been shown before suggesting an important role of the dentate nucleus in cerebellar vestibular processing [3]. In a case report Anagnostou and co-workers [1] described two patients that showed positional nystagmus with a contrast enhancing lesion of the BC in patients with MS. However, they did not find any signs of OTR in these patients. In another single case report by Thurtell and colleagues [50] a patient with B-cell lymphoma showed upbeat torsional nystagmus with a contrast enhancing lesion which they projected to the BC. They

Table 1
Comparison of the different nomenclatures of "vestibular" thalamic nuclei (adapted from Hirai and Jones, 1989 [23,25])

Hassler et al.	Hirai and Jones
Ncl. dorsomedialis / medialis dorsalis (M)	mediodorsal nucleus (MD)
fibrosus (M. fi.)	magnocellular (mc)
fasciculosus (M. fa.)	lateral
caudalis (M. c. i. and M. c. e.)	ventral
paralamellaris (M. pL.)	central lateral (CL)
Ncl. intralamellares (iLa, La M)	central lateral (CL) and paracentral nucleus (Pc)
oralis (iLa. o.)	anterior CL and paracentral nucleus (Pc)
ventralis (iLA v.)	mid. CL
interpolaris (iLa. p.)	mid. CL
caudalis (Ila. c.)	post. CL
Ncl. centralis thalami (Ce)	centre Médian (CM)
parvocellularis and magnocellularis	
Ncl. parafascicularis (Pf)	Ncl. parafasciuclaris (Pf)
Ncl. ventrocaudalis posterior externus (V. c. p. e. /Vce)	ventral posterior lateral, posterior part (VPLp)
Ncl. ventrocaudalis anterior externus (V. c. a. e. / Vce)	ventral posterior lateral, anterior part (VPLa)
Ncl. ventrocaudalis anterior internus (V. c. a. i. / Vci)	ventral posterior medial (VPM)
Ncl. ventrointermedii (Vim)	
externus (V. i. m. e.)	
internus (V. i. m. i.)	ventral lateral posterior (VLp (ventral))
Ncl. ventrooralis internus (Voi)	ventral lateral posterior (VLp (anteromedial))
Ncl. dorsocaudalis (Dc)	lateral posterior (LP)
Ncll. posterior thalami (Pu)	
Ncl. pulvinaris lateralis (Pu. l.)	lateral pulvinar nucleus (Pll)
Ncl. pulvinaris medialis (Pu. m.)	medial pulvinar nucleus (Plm)
internus (Pu. m. i.)	
dorsalis (Pu. m. d.)	
zentralis (Pu. m. z.)	
ventralis (Pu. m. v.)	
Ncl. pulvinaris ventralis (Pu. v.)	inferior pulvinar nucleus (Pli)
Ncl. pulvinaris intergeniculatus (Pu. ig.)	inferior pulvinar nucleus (Pli)
Ncl. pulvinaris suprabrachialis (Pu. sb.)	inferior pulvinar nucleus (Pli)
Ncl. pulvinaris oralis (Pu. o.)	lateral posterior (LP) and dorsal parts of Pla (anterior Pulvinar ncl.)
orolateralis (Pu. o. e.)	
oromedialis (Pu. o. m.)	
oroventralis (Pu. o. v.)	anterior pulvinar nucleus, (Pla), dorsal part

concluded that anterior SCC signals are transmitted via the BC (but also other structures such as the CVTT and MLF). Even though vasogenic edema might have been a confounding variable in their observation, the results seem plausible since no signs of interruption of other tracts (i.e., INO for MLF lesions) had been observed [50].

2.5. *Ipsilateral vestibulothalamic tract (IVTT) in humans*

An ipsilateral vestibulothalamic tract was first described by Zwergal and co-workers [51]. Evidence came from the observation that patients with anteromedial pontomesencephalic infarction showed a deviation of subjective visual vertical that was ipsiversive to the lesion which would not have been in line with the anatomical course of the MLF. In a descriptive lesion analysis they found an area adjacent to the medial lemniscus (ML) that was most commonly affected. They combined this approach with anterograde tracer injections in the vestibular nuclear complex in primates where they found labeling in the common tracts but also in a small branch adjacent to the ML confirming their clinical findings. They figured that this tract is the correlate of a three-neuron vestibulocortical tract that adds information about head and body movements to the multisensory cortical network involved in spatial orientation. They hypothesized that this tract ends in the posterolateral thalamus together with the ML (Vce/Vci/VPLa/p, VPM, see Fig. 1) but due to technical reasons the tract could not be followed up to the thalamic level [51,53]. Evidence for an ipsilateral vestibulothalamic pathway had been indicated before by Dieterich and colleagues using ^{15}O-labeled H_2O-PET [18]. Baier and co-workers [6] could not confirm these findings statistically using VLBM but also found affection of the ML in three patients in a subtraction analysis of patients with anterior paramedian pontine infarctions.

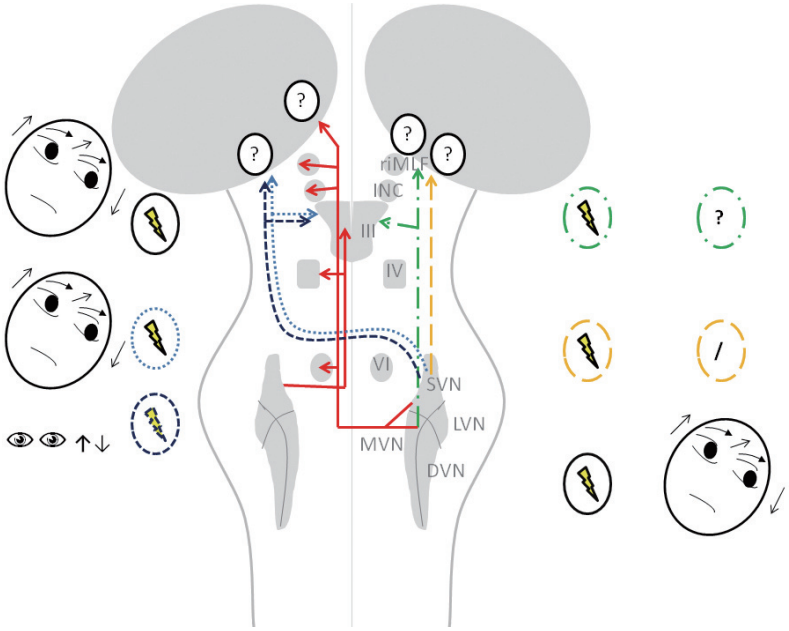

Fig. 1. : Ascending tract of Deiters (ATD), : Medial longitudinal fascicle (MLF), : Ipsilateral vestibulothalamic tract (IVTT), : Crossed ventral tegmental tract (CVTT), : Brachium conjunctivum (BC). III: Oculomotor nuclei, IV: Trochlear nucleus, VI: Abudcens nucleus, INC: Interstitial nucleus of Cajal, riMLF: rostral interstitial nucleus of the MLF, Flash: Lesioned. Lesions of the MLF: Caudal brainstem: Ocular tilt reaction ipsiversive to the lesion, rostral brainstem: OTR contraversive to the lesion; Lesion of the IVTT: Deviation of the SVV ipsiversive to the lesion; lesions of CVTT and BC: OTR contraversive to the lesion, Upbeat nystagmus; ATD: No evidence in humans. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140534)

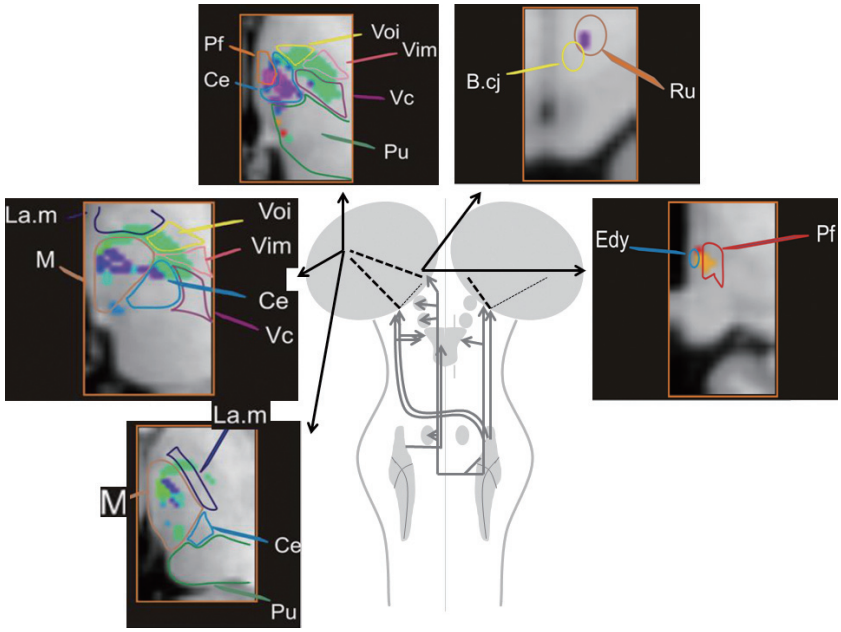

Fig. 2. Thalamic nuclei leading if lesioned to ipsiversive – (right side) or contraversive deviation of SVV (left side). Adapted from Baier et al. [4]. Figure legend: Edy: Ncl. endymalis thalami, Pf: parafascicular nucleus, Bcj: brachium conjunctivum, Ru: Ncl. ruber tegmenti, Voi: Ncl. ventrooralis internus, Vim: Ncl. ventrointermedius, Vc: Ncl. ventrocaudales, Ce: centre Médian, La. M.: Ncl. intralamellares, Pu: pulvinar nuclei, M: dorsomedial nucleus (nomenclature of Hassler, for nomenclature of Jones and Hirai see Fig. 1), dotted lines: Unknown intrathalamic pathways. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/VES-140534)

3. Vestibular thalamic nuclei in humans

Vestibular signaling and its functional importance regarding the perception of verticality and higher order sensory function (i.e. spatial orientation) in the thalamus has been a matter of debate for years. But while there is a lot of animal data on thalamic processing, data on human vestibular processing in the thalamic nuclei is sparse. Also the concurring nomenclatures make the complex interactions in thalamic processing and their anatomical localization even more difficult [36].

We will first give an overview of the two mainly used nomenclatures [23,24] and then proceed to functional imaging and lesion studies investigating the role of the thalamus in central vestibular processing.

Dieterich and Brandt [19] found in a descriptive study that lesions of the posterolateral and the paramedian thalamus lead to a deviation of the SVV either to the ipsiversive or to the contraversive side. They projected vestibular signaling in the posterolateral part of the thalamus to the ventrointermedii nuclei (Vim/VLp), the dorsocaudales nuclei (Dc/LP), the ventrocaudales posterior – and – anterior externus (Vce/VPLp and VPLa) and ventrocaudales anterior internus (Vci/VPM) nuclei [24,25]. The ventrocaudal nuclei (VPL and VPM in the "anglo-american" nomenclature) are the main thalamic targets for somatosensory processing but had already been shown to be part of central vestibular processing in animals (for review see Lopez et al. [36]). Deviation of the SVV in paramedian infarction was attributed to a common blood supply of the rostral midbrain and the paramedian thalamus through the paramedian artery (superior branch) from the P1 segment of the posterior cerebral artery (PCA) which leads to an affection of the midbrain ocular motor integration centers INC and riMLF (inferior and middle branch) [19] (for review see Schmahmann) [47]. Thus, patients with paramedian thalamic infarction also had signs of ocular tilt reaction and the deviation of the SVV was regarded to be a "side effect" of the rostral midbrain lesion.

Barra and co-workers [8] examined patients with different degrees of sensory loss (hemiplegic/hemiparetic, paraplegics) in two postural conditions. They measured the SVV in complete darkness either upright or when tilted to one side. They found that a greater deviation of the SVV in lateral body tilt, which is considered physiological (Aubert effect), was preserved when hemiparetic or hemiplegic patients were tilted to the side without sensory loss, but was abolished when tilted to the affected side and in patients with paraplegia. The effect was also correlated with the severity of the lesion. A lesion analysis of patients with and without SVV modulation found that the lesions were mostly centered on the ventroposterior lateral thalamic nuclei (Vce/VPLp/a) when the SVV modulation was disturbed. Thus the authors concluded that the ventroposterior part of the thalamus is an area of multisensory signal integration before reaching the multisensory cortical areas. This observation was based on subtraction analysis but a statistical association of damaged voxels and disturbed modulation of verticality perception was not examined. Even more importantly no pure thalamic infarctions had been included in the analysis [8].

Using FDG-PET, Bense and co-workers [10] found a significant increase of rCBF (regional cerebral blood flow) in the bilateral posterolateral thalami while cortical signal increase was measurable in the left hemisphere. This points towards a dichotomy of vestibular pathways to the thalamic level and signal integration in the thalamus in patients with acute vestibular neuritis. No indication was made which thalamic nuclei were affected by the increase in rCBF. Bilateral thalamic activation was also seen in healthy right-handers after galvanic stimulation of the right mastoid using fMRI [11]. Activation there was centered on paramedian and posterolateral thalamic regions. Dieterich and colleagues [18] found a dominance for vestibular cortical function in the non-dominant hemisphere and also dependence on the side of vestibular stimulation. In their study activation was stronger ipsilateral to the irrigated ear (caloric irrigation with warm water) and in the ipsilateral and non-dominant hemisphere. Interestingly they found differing activation patterns in the thalamus. When right-handers were stimulated in the right ear, thalamic activation patterns involved the posterolateral and posteromedial thalamus but contralaterally only the posterlateral thalamic structures. In left-handers, stimulation of the left ear activated the anterior and parmedian thalamic regions while right ear stimulation induced activation of the anteromedial thalamic regions bilaterally. Thus, the side of stimulation and handedness seem to affect subcortical and cortical vestibular processing. The functional meaning and exact location of the thalamic activation were not mentioned in this study which focused on the cortical vestibular network.

In patients with infarctions of the posterolateral part of the thalamus, caloric vestibular stimulation with warm water was performed and the cortical activa-

tion pattern was analyzed using $H_2^{15}0$-PET [17]. In this study the role of the thalamus in relaying vestibular information could be confirmed as activation was reduced in both hemispheres and the effect of the stimulation side and the hemispheric dominance persisted. Clinical signs of the thalamic infarction were not regarded in this activation study. Retrospectively it would be very interesting to correlate the activation/deactivation patterns with clinical parameters of perceptual dysfunction.

In a recent study our group investigated whether there are distinct anatomical regions in the thalamus involved in otolith processing that lead, when damaged, either to an ipsiversive or contraversive tilt of SVV [4]. By using voxel-based lesion behavior mapping (VLBM) we found that contraversive tilt was associated with lesions of the superior parafascicular nucleus (Pf), Ncl. dorsomedialis (M/MD), Ncl. intralamellares (La. M/CL, Pc), Ncl. centrales thalami (Ce/CM), Ncl. posterior thalami (Pulvinar, Pu), Ncl. ventrocaudalis externus (Vce; /VPL/VPM), Ncl. ventrointermedius (Vim/VL), Ncl. ventrooralis internus (Voi/VL), whereas lesions statistically associated with ipsiversive tilt were located more medial and inferior in the inferior parafascicular nucleus (Pf) and the junction zone of ncl. ruber tegmenti and brachium conjunctivum. Anatomical localization within the thalamus was examined using the stereotaxic atlas of the Thalamus by Schaltenbrandt and Wahren [46].

Supporting evidence for these findings so far stems only from animal studies where ipsilateral vestibular projections have been found to project to the red nucleus and the parafascicular nucleus (among others) in the rat [39,48] and macaque [40]. On the other hand many studies have found vestibular responsive neurons in the contralateral VPL/VPM (Vce, Vci) and VL (Vim, Voi) region (for review see Lopez et al. [36]).

In patients with deep brain stimulation (DBS) for essential tremor in the Vim, disequilibrium is a common side effect [16]. Ceballos-Baumann and colleagues [16] showed that Vim stimulation leads to a decrease of rCBF in the contralateral retroinsular cortical areas. In their study only patients with stimulation of the left Vim were considered. However, no implication on the functional significance of this finding was given. More recently Baier and co-workers showed in patients with Vim DBS for essential tremor that otolith dominated verticality perception could directly be modulated by turning the stimulator "on" or "off" [7].

4. Functional significance of thalamic lesions regarding higher order sensory function – Thalamic astasia, pusher syndrome and spatial neglect

As higher order visual function is well defined, concordantly higher order vestibular function can be defined [12]. The latter involves complex perceptual, sensorimotor and behavioral facets that exceed basic perceptions such as body motion, motor responses and vestibulo-ocular and vestibulospinal reflexes. Between them it is possible to identify some similarities and differences. One difference seems to be that higher order vestibular function involves other sensory modalities as well. Both sensory modalities involve higher cognitive function like attention, spatial orientation and navigation or spatial memory. This makes differentiation of higher order visual and vestibular function difficult at times as is evident when studying phenomena like spatial neglect. Therefore, the question whether these disorders can be attributed to a vestibular tone imbalance at different levels of the vestibulo-cortical signal transmission has been raised in the case of thalamic astasia, pusher syndrome and spatial neglect (Brandt and co-workers [12]).

4.1. Thalamic astasia

The finding of thalamic astasia was first described by Masdeu and co-workers in 15 patients with thalamic lesions [38]. Patients with thalamic astasia have a tendency to fall backwards, forward or to the affected side even though no marked sensory loss or paresis is present. In their study the most common lesion site was the posterolateral region of the thalamus but in some patients other parts of the thalamus or the suprathalamic white matter were also involved. Many patients had also signs of spatial inattention, Babinski sign and imbalance in muscle tone. Unfortunately no measurement of vestibular function at the thalamic level (i.e. SVV) had been carried out to investigate whether this finding reflects a vestibular tone imbalance. Recurrent falls after thalamic lesions without relevant paresis had been reported much earlier by Hassler in patients who had received thalamotomy [23]. Since then some case reports have been published that also found thalamic astasia in patients with thalamic hemorrhage or infarction mostly centered on the posterolateral thalamus [32,35] and in one case with an isolated infarction of the Centre Médian nucleus [20]. In the latter case report measurements of the SVV had been carried out

which showed a consistent tilt of 6° to the right in left centre median infarction suggesting a vestibular tone imbalance towards the contralateral side. However, so far there is no statistical evidence of the anatomical localization of thalamic astasia in isolated thalamic infarction. In a larger sample of 37 patients with pure thalamic infarctions with regard to vestibular function thalamic astasia was not found [4] whereas Dieterich and co-workers found symptoms consistent with thalamic astasia in 2 of 11 patients with SVV tilts in thalamic infarctions [19].

4.2. Pusher syndrome

In contrast to thalamic astasia, Pusher syndrome occurs in patients who have relevant hemiparesis. The pathognomonic findings are that these patients push to the side of the paresis and resist attempts to correct their posture. Pérrenou and co-workers [43] studied 80 patients with a first ever stroke with regard to their perceived visual (SVV), haptic (haptic vertical, SHV) and postural vertical (SPV) as well as clinical parameters such as lateropulsion and pushing behavior. They could show that patients with brainstem lesions showed lateropulsion as a main sign (active lateral tilt: ipsilateral in caudal brainstem lesions and contralateral to the lesion in rostral brainstem and hemisphere strokes). The perceptual correlate tilt of the SVV was more than that of the SHV, while the postural vertical was impaired in only one patient. Unfortunately only six patients with brainstem infarction were tested. In hemisphere stroke the tilt of the SVV was also the most common sign but almost half of the patients also showed tilts of the postural vertical. Postural vertical tilt was correlated with right sided lesions, size of a lesion in the right hemisphere and severity of the postural disorder, while deviation of the SVV and SHV was not. Patients with pushing behavior showed transmodal tilt (tilt of SVV, SPV and SHV) and compared to patients without pushing behavior, the gravitational tilt, always contraversive to the lesion, was more severe [43].

In their comparison of lesion location and SPV tilts, the authors found that SPV tilts were linked to greater size of a lesion and to lesions in the thalamus and the parietal cortex [43]. In their analysis specific thalamic regions involved are not mentioned. Therefore, it cannot be differentiated whether this finding represents a role of the thalamus in postural vertical perception or the disturbance of thalamocortical networks. Another limitation is that patients were tested several weeks after stroke. Further, there is no mention of the time of the MRI scan thus it seems possible that function after rehabilitation and partial recovery was compared with the acute stage MRI lesion.

In contrast to these findings, Karnath and co-workers [26,28,30,49] described that patients with pushing behavior had ipsilesional tilts of postural vertical perception while SVV perception was (relatively) spared. They could show that lesions that involve the thalamus (mainly hemorrhages of the posterior thalamus) may lead to pusher syndrome but also cortical lesions involving areas such as inferior frontal gyrus (IFG), middle temporal gyrus (MTG), precentral gyrus, inferior parietal lobule (IPL) and parietal white matter and the superior longitudinal fascicle (SLF). It is, however, not clear to what extent accompanying lesions of e.g. the internal capsule are involved in pusher behavior especially in the case of thalamic hemorrhage. With regard to the stronger impairment of postural vertical compared to visual vertical they assumed that pusher behavior is a result of the dissociation of different sensory cues, namely visual/vestibular and graviceptive information and concluded that there must be an independent graviceptive system located in the posterolateral thalamus. The mean average tilt of SVV, however, was also pathological in their study, even though to a lesser extent than the SPV. It remains unclear why the tilts of SPV were ipsiversive to the lesion (and contraversive to the pushing behavior) and why they were abolished when patients could see their surroundings which is not the case when pushing is observed clinically. More compelling seems to be the theory that a severe transmodal sensory bias causes pushing behavior because of the lack of multisensory influx in the lesioned hemisphere. This would point either toward higher order sensory processing in the thalamus itself or involvement of relevant white matter tracts important for integration of sensory signals.

4.3. Spatial neglect

Spatial neglect is a disorder of spatial orientation and exploration where patients fail to explore the contralesional hemispace and do not react to stimuli presented in that hemifield. Neglect patients show a clinical behavior (deviation of the head and eyes to the side of the lesion) that is similar to that of a vestibular tone imbalance as can be induced by peripheral vestibular stimulation. Cortical regions that are damaged in neglect patients overlap with the areas presumed to be the cortical multisensory vestibular integration centers [13, 27].

Spatial neglect has also been reported over the years in patients with subcortical infarction involving the thalamus [31,34] Karnath and co-workers [29] used subtraction analysis in patients with strokes involving the thalamus who did or did not show signs of neglect. In their analysis the medial pulvinar and posterolateral thalamic nuclei were the areas most commonly damaged. It is noteworthy, however, that most lesions in their sample seem to have involved the posterior part of the internal capsule as well and were not restricted to the thalamus alone. In a recent study by Baier and colleagues clinical signs of spatial neglect according to the signs of Fruhmann Berger and colleagues [21] were not observed in a sample of 37 patients with isolated infarction of different thalamic nuclei [4]. Standardized paper-pencil testing for neglect signs was carried out only in a subset of patients. To our knowledge so far a clear association of disturbed perception of verticality and neglect has not been demonstrated at the thalamic level. Whether neglect is also a sign of an isolated thalamic lesion remains a matter of debate as does the association of vestibular tone imbalance measured with the SVV and spatial neglect.

5. Thalamic processing of vestibular information

Vestibular information is conveyed via different ipsilateral and contralateral brainstem pathways to the ipsilateral and contralateral thalamus. While in the contraversive pathways ocular motor control is also included, the ipsilateral projections seem to convey mostly perceptual information. At the thalamic level only verticality perception is modulated. In a recent study it was shown for the first time that thalamic centers for verticality perception that lead, when damaged, to a vestibular tone balance either to the ipsiversive or contraversive side are represented in two distinct anatomical localizations and thus represent a dichotomy of vestibular signal processing on the level of the thalamic nuclei. No correlation with disturbed somatosensory function could be found in these nuclei [4].

The localization of higher order sensory integration is still unclear. It is conceivable that, like different vestibular signals converge on their way to the thalamus, further integration of sensory information follows as thalamocortical neurons pass other thalamic nuclei and the internal capsule. Higher order deficits such as pushing behavior or spatial neglect would therefore necessitate the involvement of ipsilateral thalamocortical neurons that provide not only the integration of multisensory signals but also the transformation of these signals into space coordinates that create a sense of body orientation in space.

Since the bilaterality of cortical signals is preserved even in patients with lesions of thalamic vestibular structures [17] the localization and functional relevance of interhemispheric communication is also not yet defined and is a further aspect for future research.

6. Conclusions

Five brainstem tracts conveying vestibular information to the cortex were described in animal studies. For four of them there is also evidence in humans deriving mostly from lesion studies.

With the evolution of MRI imaging techniques (such as diffusion tensor imaging, DTI) it will become easier to identify the localization of these tracts and possibly their terminations in the oculomotor nuclei and/or the thalamic nuclei.

Different thalamic nuclei appear to be involved in processing vestibular information in two distinct anatomical areas. Damage to these areas leads to a disturbed perception of verticality either to the ipsiversive or to the contraversive side. These findings point towards a dichotomy of vestibular processing in the thalamus. So far, there is no valid information which brainstem tracts end in which specific thalamic nuclei in humans.

There is still great debate over the issue whether pusher syndrome or spatial neglect can be induced by an isolated thalamic lesion. Since many patients with pusher syndrome also show signs of spatial neglect this leads to the question of the correlation between these two phenomena.

Finally, no great emphasis has yet put on the question of differentiating upward (vestibulo-thalamo-cortical-) and downward (cortico-thalamo-vestibular) transmission.

Therefore, future research should focus especially on transmission from brainstem tracts to the thalamus, the functional relevance of thalamic signal integration with regards to higher order sensory integration and the differentiation of upward and downward vestibular signal processing in humans.

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Conflicts of interest

None.

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