

Involvement of the human ventrolateral thalamus in olfaction

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Abstract It is widely assumed that the thalamus is not involved in olfaction. The ventrolateral thalamus is, however, closely connected to the contralateral cerebellum, which is involved in the sense of smell based on findings from functional imaging studies and findings of olfactory deficits in patients with cerebellar disease. We hypothesized that olfactory deficits following lesions of the ventrolateral thalamus may be similar to olfactory deficits following cerebellar lesions. Fifteen patients with a focal thalamic lesion involving the ventrolateral thalamus were examined and compared to 15 patients with a focal cerebellar lesion and 15 healthy controls. A detailed olfactory

test (“Sniffin’ Sticks”) was used to assess different olfactory functions separately for each nostril. In the group of patients with a lesion of the ventrolateral thalamus, an impairment of the odor threshold was found at the ipsilateral nostril, consistent with the unilateral orientation of the olfactory system in the telencephalon. In the group of patients with a cerebellar lesion, an olfactory deficit at the contralesional nostril emerged. In controls, no significant side difference was found. The involvement of the ventrolateral thalamus in olfaction is comparable to that of the cerebellum in respect to odor threshold. Further study is needed to assess if these findings are related to an impairment of an olfactomotor loop. Present evidence for this hypothesis is indirect. Effects were subclinical as none of the patients reported olfactory disturbance. The results suggest that the cerebello-thalamic axis plays an adjuvant role in olfaction.

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Introduction

At first glance, the thalamus does not appear to be involved in olfaction, as olfactory information reaches the cortex without an obligatory thalamic relay, which is in contrast to all other sensory modalities [1–3]. However, several lines of evidence point to an indirect involvement of the mediodorsal (MD) thalamus in the sense of smell [4–9]. In contrast, the role of the ventrolateral (VL) thalamus in olfaction is unclear at present. Exploring the involvement of the VL thalamus in the sense of smell is of interest to obtain a better insight into the neuronal network of olfaction, which is still an understudied area of clinical research.

The VL thalamus and the cerebellum are traditionally considered to be part of the motor-control system. Yet, involvement of the cerebellum in olfaction is suggested by cerebellar activation described in functional imaging studies of olfaction [10–13] and olfactory impairment in patients with cerebellar disease [14–16]. The VL thalamus is functionally closely connected to the contralateral cerebellum, and is therefore also referred to as the “cerebellar thalamus” [17–19]. For example, lesions of the VL thalamus lead to ataxia of the contralesional limbs reminiscing motor deficits ipsilateral to focal cerebellar disease [20–22]. Comparable to motor deficits, we hypothesized that olfactory deficits following a lesion of the VL thalamus may similarly be found to olfactory deficits with cerebellar lesions. In contrast to other sensory modalities, the olfactory system has an ipsilateral orientation at the telencephalon [3]. Therefore, we anticipated olfactory deficits at the nostril ipsilateral to a lesion of the VL thalamus. To investigate this hypothesis, olfactory function was tested in patients with a lesion of the VL thalamus and compared to patients with a focal cerebellar lesion and healthy controls.

Methods

Patients with a single vascular lesion involving the VL thalamus or the cerebellum were included. Additionally, two patients following surgical removal of a benign cerebellar tumor were examined. Exclusion criteria were past or present tobacco smoking, use of medication that act on the central nervous system, deformities, infections, or inflammatory diseases of the nose or sinuses, psychiatric diseases, involuntary movements, or brain lesions outside the thalamus or the cerebellum. Altogether, 15 patients with a thalamic lesion (Table 1), 15 patients with a cerebellar lesion (Table 2), and 15 healthy controls matched for age and sex (4 women, 11 men; age 60.3 ± 9.6 years) were examined. Major pathology of the nasal cavities was excluded with anterior rhinoscopy. Furthermore, rhinomanometry was used to assess air flow through the nostrils during normal breathing, which was found not to be different between groups (Table 3 in Online Resource). The examiner was blinded towards the participants' group and side of the brain lesion. Additionally, participants were informed about the background of this study but not given details related to the hypothesis assessed. Furthermore, during olfactory testing the participants did not receive any feedback about their performance.

Olfactory testing

The “Sniffin’ Sticks” [23, 24] were administered separately for each nostril to assess odor threshold, odor

discrimination, and odor identification (for details of the olfactory testing see Online Resource).

Brain imaging

The axial images of the magnetic resonance tomography or the computer tomography made during routine care were used to localize the brain lesion (for examples please see Fig. 1). The location and extent of the lesion was manually entered into MRicroN software (Lazarus INC, USA, Version 15).

Neuropsychological testing

Basic memory functioning was assessed using the logical memory tests, and the digit span tests [25]. The Multiple Choice Vocabulary Intelligence test [26] was also performed.

Statistics

Non-parametric Kruskal–Wallis test for repeated measurements was used to compare the side difference between nostrils in the olfactory tests in the three groups. Additionally, the Wilcoxon rank sum test was applied to compare results of the ipsilesional nostril with those of the contralesional nostril in each group. *P* values <0.05 were regarded as significant. The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki (1964). The local ethical committee approved this study. All participants gave written informed consent before testing.

Results

In the group of patients with a thalamic lesion, an olfactory impairment at the ipsilesional nostril was found as indicated by a lower score of the ipsilesional nostril compared to the score of the contralesional nostril (Fig. 2a–c). In contrast, the patient group with a cerebellar lesion had an olfactory deficit at the contralesional nostril, while no side difference was found in the group of healthy controls.

The Kruskal–Wallis test yielded a significant difference between the three groups for odor threshold ($p < 0.01$) and odor identification ($p = 0.04$), while there was no difference in odor discrimination ($p = 0.13$). The Wilcoxon rank sum test revealed a significant difference between the two nostrils for odor threshold in patients with a cerebellar lesion ($p < 0.01$) and in patients with a thalamic lesion ($p < 0.01$), while a significant difference between the two nostrils on the odor identification task was only found in patients with a cerebellar lesion ($p = 0.01$).

Table 1 Clinical characteristics of patients with a thalamic lesion

Demographics				Clinical deficit at the contralateral side				Extent of the brain lesion				Olfactory deficit			
ID	Sex	Age (years)	Assessment after lesion (months)	Lesion type	Lesion side	Ataxia	Hypesthesia	Slight paresis	VL thalamus	Lesion posterior to VL thalamus	Lesion anterior to VL thalamus	Odor discrimination deficit	Odor threshold deficit	Odor identification deficit	
T2	M	38	28	I	L	Arm			X						
T11	F	75	1	H	R	Arm		Arm	X			+			
T12	M	50	1	I	R	Arm		Arm	X				+	+	
T13	F	67	88	I	L	Arm			X				+	+	
T1	M	77	1	I	L	Arm/Leg	Arm/Leg		X	X		+	+		
T5	F	47	13	I	L		Arm		X	X		-			
T6	M	71	68	I	L		Hand		X	X				+	
T7	M	63	67	I	R	Arm	Arm/Face		X	X				-	
T8	F	52	27	I	R		Face/Arm/Leg		X	X				+	
T10	M	44	1	I	R	Arm/Leg	Face/Arm/Leg	Leg	X	X		+	+		
T14	M	53	6	I	R	Arm	Face		X	X		+	+		
T15	M	57	1	I	R	Arm/Leg	Face/Arm/Leg		X	X		+	+		
T3	M	43	38	I	L				X		X				
T4	M	69	24	I	R	Arm/Leg			X		X			-	
T9	M	58	76	I	L				X		X			-	

ID, identification of individual patients; M, male; F, female; H, hemorrhage; I, ischemia; R, right hemispheric lesion; L, left hemispheric lesion; ataxia, presence of ataxia was diagnosed based on the finger-to-nose test and heel-to-shin test, respectively; VL, ventrolateral; +, olfactory deficit at the ipsilesional nostril and a side difference between the ipsilesional nostril and the contralateral nostril was larger than twice the standard deviation found in controls; -, olfactory deficit at the contralateral nostril and a side difference between the ipsilesional nostril and the contralateral nostril was larger than twice the standard deviation found in controls. Reconstruction of the extent of a thalamic lesion was based on the Schaltenbrand and Wahren atlas [42]

Table 2 Clinical characteristics of the patients with a cerebellar lesion

Demographics						Clinical deficit at the ipsilateral side			Olfactory deficit		
ID	Sex	Age (years)	Assessment after lesion (months)	Lesion type	Lesion side	Ataxia	Hypesthesia	Slight paresis	Odor discrimination deficit	Odor threshold deficit	Odor identification deficit
C1	M	67	48	H	R	Arm				+	
C2	M	78	1	H	R	Arm					+
C3	M	63	53	I	L				+	+	+
C4	F	65	65	I	L	Arm/Leg					+
C5	M	63	50	I	R	Arm				+	+
C6	F	71	18	I	L	Arm/Leg				+	+
C7	M	57	1	Npl	L	Arm			+	+	
C8	M	69	321	I	L	Arm/Leg			–	+	
C9	M	58	40	I	L	Arm/Leg			+	+	
C10	F	71	24	I	L	Arm			+	+	+
C11	F	71	39	I	R				+	+	+
C12	M	47	6	I	R	Leg				+	+
C13	M	54	7	I	L					+	+
C14	M	52	15	I	R	Arm/Leg				+	
C15	M	57	1	Npl	R	Arm/Leg				+	

ID, identification of individual patients; *M*, male; *F*, female; *H*, hemorrhage; *I*, ischemia; *Npl*, neoplasm; *R*, right hemispheric lesion; *L*, left hemispheric lesion; ataxia, presence of ataxia was diagnosed on the basis of the finger-to-nose test and the heel-to-shin test, respectively; +, olfactory deficit at the contralesional nostril and a side difference between the ipsilesional nostril and the contralesional nostril was larger than twice the standard deviation found in controls; –, olfactory deficit at the ipsilesional nostril and a side difference between the ipsilesional nostril and the contralesional nostril was larger than twice the standard deviation found in controls

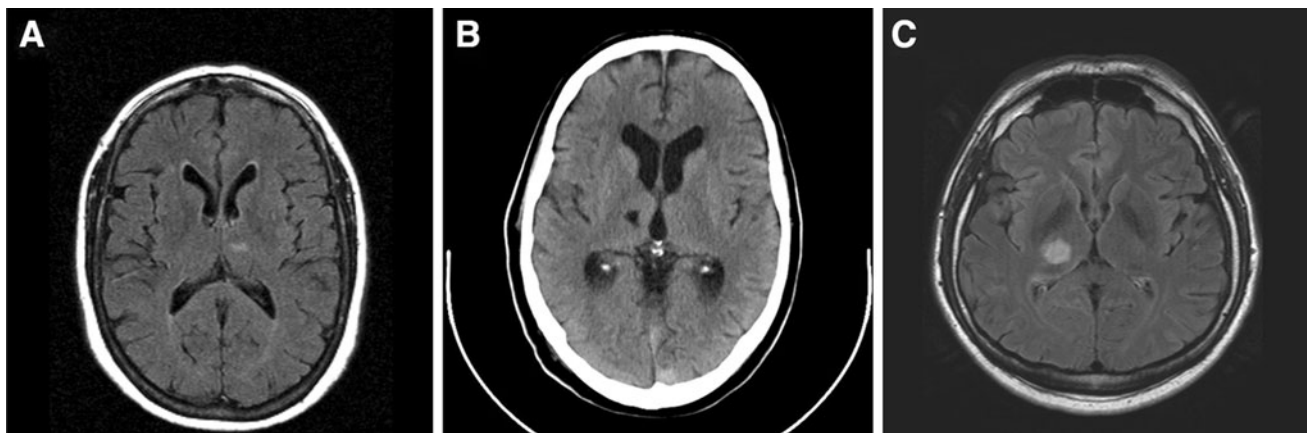


Fig. 1 Examples of the brain scans that were used to identify the thalamic lesions. **a** Magnet resonance image (MRI) of patient T2 in Table 1 with a lesion of the VL thalamus only, **b** Computer tomography of patient T4 in Table 1 showing a lesion of the VL

thalamus, which extends into the anterior thalamus, **c**. MRI of patient T10 in Table 1 showing a thalamic lesion involving the VL thalamus and the posterior thalamus. The thalamic strokes were only seen on one slice, as they extended primarily into the horizontal direction [41]

In the analysis of the imaging data, patients with a focal lesion of the thalamus and an ipsilesional odor threshold deficit were found to have their largest overlap in the VL thalamus, while cerebellar patients with a contralesional odor threshold deficit were found to have the largest overlap of their lesion in the cerebellar hemispheres (Fig. 3 in Online Resource). Lesion size (number of voxels) did not correlate with the olfactory deficits in either patient

group ($p > 0.25$, Spearman rank correlation). For subgroup analysis, the patients with a thalamic lesion were divided into three groups: (1) patients with a lesion restricted to the VL thalamus, (2) patients with a lesion of the VL thalamus that extended into the posterior thalamus, and (3) patients with a lesion of the VL thalamus that extended into the anterior thalamus (Table 1). None of the three subgroups exhibited a distinguishable pattern (Table 1; odor

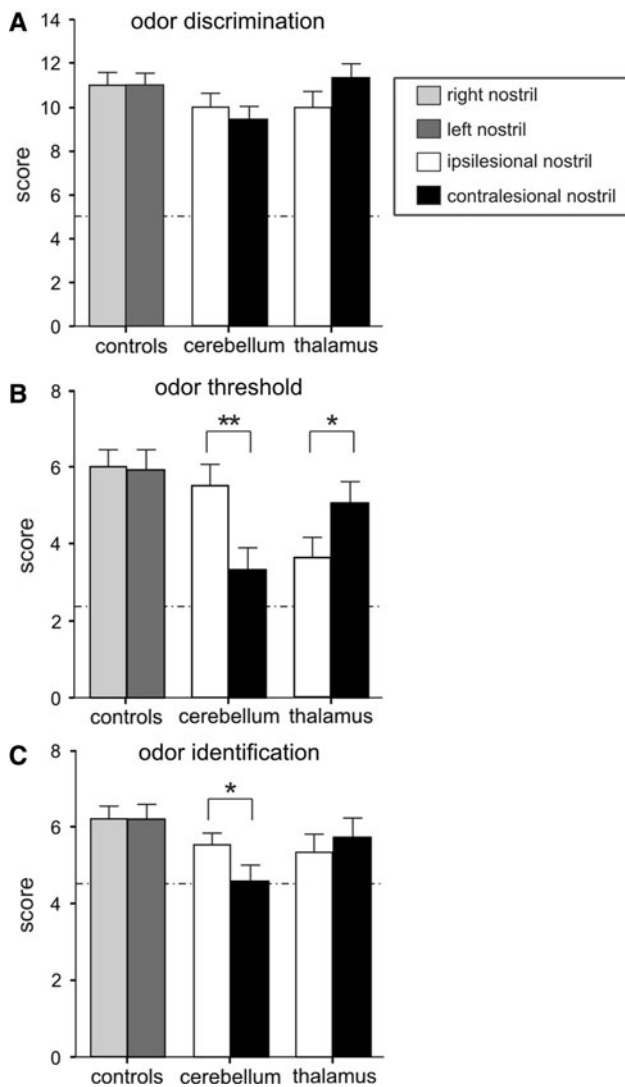


Fig. 2 Results from the Sniffin' Sticks test. **a** Odor discrimination task, **b** odor threshold task, and **c** identification task. Dashed lines depict the tenth percentile, indicative for hyposmia [19]. Controls, group of healthy controls; cerebellum, group of patients with a cerebellar lesion; thalamus, group of patients with a thalamic lesion involving the VL thalamus; * $p < 0.05$ and ** $p < 0.01$ revealed by Wilcoxon rank sum test

discrimination: $p = 0.76$, odor threshold: $p = 0.71$ or odor identification: $p = 0.12$; Kruskal–Wallis test). Although thalamic patients had their stroke in the territory of the thalamo-geniculate arteries [27], findings upon clinical examination varied, i.e. they may have ataxia, hypesthesia, or a slight paresis [20–22]. Subgroup analysis indicated that patients with a thalamic lesion and ataxia but without a paresis had a larger odor threshold impairment at the ipsilesional nostril (side difference 2.1 ± 2.2) than did patients without ataxia and without paresis (side difference 0.3 ± 0.8) ($p = 0.04$, Wilcoxon rank sum test), while all other comparisons (with/without hypesthesia or paresis) were not different (p values > 0.15).

The analysis of the neuropsychological test revealed a significant difference on the digit span forward task ($p = 0.04$) and digit span backward task ($p = 0.01$) where cerebellar patients performed the worst (Table 4 in Online Resource). Spearman rank correlation comparing performance in the olfactory tests and performance with the neuropsychological assessment, septal orientation (towards the contralesional or ipsilesional nostril as assessed with anterior rhinoscopy), or air flow with normal breathing did not reveal any significant correlations.

Discussion

Using a standardized approach, this study demonstrates involvement of the VL thalamus in olfaction. In the group of patients with a lesion of the VL thalamus, an olfactory deficit was found at the ipsilateral nostril consistent with the unilateral orientation of the olfactory system in the telencephalon [3, 28]. Patients with a cerebellar lesion had the opposite, an olfactory deficit at the contralesional nostril, which is in accordance with the functional bond of the cerebellum to the contralateral VL thalamus [17–19].

Involvement of the cerebellum and the VL thalamus in olfaction appears surprising at first. However, the cerebellum receives information from different sensory modalities, to monitor and modulate behavior in order to optimize sampling of sensory information [29]. This may also be true for the role of the cerebellum with respect to the sense of smell [10, 16, 30]. The cerebellum receives projections from the primary olfactory cortex [31], as well as the trigeminal nerve [32] and projects via the contralateral VL thalamus to multiple cortical areas involved in olfaction [18, 33, 34]. The major termination zones of cerebellar projections to the thalamus are the nucleus ventrointermedius and the nucleus ventrooralis posterior of the human VL thalamus [18]. These nuclei project to the motor cortex [33, 34] where the pyramidal tracts originate. These tracts are also important for the movements of the diaphragm [35], which, as the principal muscle of inspiration, is also important for sniffing.

These brain structures may be part of an olfactomotor loop. Within this circuit, the cerebellum is believed to maintain a feedback loop that regulates sniff volume inversely proportional to odor concentration allowing for optimal collection of olfactory information [10, 16, 36]. Impaired functioning of this loop may have hampered patients taking more vigorous sniffs at low n-butanol concentrations to detect the odor resulting in the odor threshold impairment found. In this study, we were not able to control or assess sniff volume on-line. Evidence that the odor threshold impairment in patients with a lesion of the VL thalamus may be related to an impairment of a

cerebellar (olfactomotor) loop is indirect. Subgroup analyses suggest that the odor threshold impairment in patients with a thalamic lesion is related to ataxia, a cerebellar motor deficit. Additionally, this odor threshold impairment is not related to hypesthesia. In patients with a thalamic lesion, hypesthesia (if present) was at the contralesional side while the odor threshold impairment was found at the ipsilateral nostril. Furthermore, the olfactory deficits are not caused by a blockade of the nostrils because airflow through the nostrils with normal breathing was not different between groups. In future studies, the assessment of olfactomotor functioning through the use of a fixed-sniff method [16] and the assessment of olfactory event-related potentials [37] may provide further support for this view. Another experiment may be to puff an odor into the nostril without sniffing. Following this line of reasoning, the odor threshold deficit should disappear with this test.

The odor identification impairment in the group of patients with a cerebellar lesion is consistent with reports of olfactory deficits in patients with cerebellar disease [14–16]. This impairment may be related to a disturbance of cerebellar projections to cortical areas involved in processing of cognitive functioning. These pathways were possibly spared from the thalamic lesions as we did not find an odor identification deficit in patients with a thalamic lesion. Cerebellar projections to subcortical structures such as the hippocampus [38, 39] may be involved in odor identification and are therefore not affected by a thalamic lesion. Deficits in the odor discrimination task were not found in any of the two patient groups. As a possibly less complex task, it involves the allocation of cognitive resources that can compensate for the subtle memory impairments found.

The comparison of the three thalamic subgroups revealed no difference of the olfactory deficits. This is possibly because all patients had a lesion that involved the VL thalamus. Lesion size did not correlate with olfactory impairment, which is in accordance with past findings with respect to cerebellar lesions [16]. The location rather than the size of a cerebellar lesion is crucial for causing a deficit [40]. Therefore, the comparison of patients with and without a lesion of the VL thalamus may disclose a correlation between location of a thalamic lesion and olfactory deficit. A case report seems to support this idea. A lesion of the MD thalamus lead to a disturbance of odor discrimination [7], while a lesion of the VL thalamus (this study) lead to odor threshold impairment.

In conclusion, the findings suggest involvement of the VL thalamus in olfaction. As none of the patients reported olfactory disturbance, the cerebello-thalamic axis may play an adjuvant role in olfaction.

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Conflict of interest statement There are no conflicts of interest to be disclosed.

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