Are signs of ocular tilt reaction in patients with cerebellar lesions mediated by the dentate nucleus?

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A sensitive clinical sign of a vestibular tone imbalance in the roll plane is the ocular tilt reaction (OTR), a combination of skew deviation, ocular torsion and head and perceptual tilts such as tilts of the subjective visual vertical (SVV). Of these OTR components tilts of SVV are the most frequent. While these signs are regularly seen in patients with unilateral brainstem lesions, only a few case studies are available on their occurrence in patients with cerebellar lesions. Thus, the question arises whether cerebellar structures may be involved in contra- and/or ipsiversive tilts of the perceived vertical and other signs of OTR. We used lesion-mapping techniques in a total of 31 patients with acute cerebellar strokes, all showing at least a significant tilt of SVV. Twenty-three patients had a contraversive tilt of the SVV; they were compared with eight patients with ipsiversive tilts. MRI/CT lesion mapping revealed that in patients showing contraversive signs of OTR in general and contraversive SVV tilts in particular the dentate nucleus was the commonly damaged structure. In contrast, in ipsiversive signs of OTR, the dentate nucleus was spared and lesions were located in the biventer lobule, the middle cerebellar peduncle, the tonsil and the inferior semilunar lobule. These data suggest that the dentate nucleus is a critical anatomical structure within the cerebellum, belonging to a network involved in vestibular processing such as the perception of verticality. Therefore, a lesion of the dentate nucleus can lead to tilts of the SVV in the contraversive direction, i.e. a vestibular tone imbalance to the contralateral side, whereas cerebellar lesions excluding the dentate nucleus can induce a tone imbalance to the ipsilesional side.

Keywords: cerebellum; stroke; ocular tilt reaction; dentate nucleus

Abbreviations: MNI = Montreal Neurological Institute; OT = ocular torsion; OTR = ocular tilt reaction; SD = skew deviation; SVV = subjective visual vertical; VOR = vestibulo-ocular reflex; VN = vestibular nucleus


Introduction

Clinical signs of a vestibular tone imbalance in the roll plane are the complete ocular tilt reaction (OTR) (Westheimer and Blair, 1975) or its components, consisting of the triad of head tilt, ocular torsion (OT) and skew deviation (SD), as well as tilts of the perceived subjective visual vertical (SVV). OTR and its components are caused by an imbalance in the vestibulo-ocular reflex (VOR) either due to a unilateral peripheral vestibular deficit such as a vestibular neuritis (Halmagyi et al., 1979) or a unilateral lesion of the central vestibular pathways in the brainstem. Brainstem lesions caudal to the pons affecting the vestibular nerve and vestibular nucleus (VN) cause ipsiversive signs of OTR, whereas lesions rostral to the pontine level affecting the medial longitudinal fasciculus and interstitial nucleus of Cajal cause contraversive signs of OTR (Halmagyi et al., 1990; Dieterich and Brandt, 1993a). Of these components, tilts of the perceived SVV are the most frequent (Brandt and Dieterich, 1994). While SD, OT and tilts of perceived SVV are regularly seen in patients with unilateral brainstem lesions, there are only a few case studies available on its occurrence in patients with cerebellar lesions (Mossmann and Halmagyi, 1997; Min et al., 1999; Lee et al., 2005). The study by Mossman and Halmagyi (1997) suggests that loss of inhibition due to the lesioned nodulus leads to an increase in tonic resting activity of secondary otolith neurons in the ipsilesional VN, and thus, to a contraversive OTR. This is in agreement with older stimulation studies in animals and humans, which gave evidence that SD and contraversive head tilt occur with cerebellar ‘lesions’, whereas ipsiversive head tilt occurs with cerebellar ‘stimulation’ (Dow, 1938; Nashold et al., 1969). Another model postulates that the vestibulo-cerebellum modulates activity in otolith-ocular connections so that in response to static
The present study used well-established lesion analysis techniques (Rorden and Karnath, 2004) to investigate the issue of defining the key area(s) typically associated with contra- or ipsiversive signs of OTR in humans. Thus, the question arises as to whether abnormalities of the VOR in the roll plane in general and the tilt of perceived SVV as the most frequent sign in particular can be found in purely cerebellar lesions and, if so, which cerebellar structures may be involved.

The present study used well-established lesion analysis techniques (Rorden and Karnath, 2004) to investigate the issue of defining the key area(s) typically associated with contra- or ipsiversive signs of OTR in cerebellar lesions. In systematically examined patients with acute predominantly unilateral cerebellar infarctions over the past 5 years, we performed a lesion subtraction analysis between a group of patients with contraversive signs of OTR and a comparison group with ipsiversive signs who were comparable with regard to demographic and clinical data, except for the direction of the critical symptoms, the signs of OTR.

**Methods**

We found 23 consecutively admitted patients with unilateral cerebellar infarction who presented with a *contraversive* tilt of the static SVV (21 patients with pure unilateral infarction, and two patients with predominantly unilateral lesions that slightly extended into the opposite tonsil or the central lobule). Ten patients had lesions on the left and 13 patients had lesions on the right. We combined all the patients and flipped the lesions to the right. The patients with ipsiversive signs of OTR represented the ‘comparison’ group (seven patients with pure unilateral infarction, and one patient with predominantly unilateral lesion that extended slightly into the opposite inferior semilunar lobule and the tonsil). Since all of the patients admitted to our hospital with acute cerebellar strokes showed tilts of SVV, we used these as the criteria to define two groups. All neurological defects were present with the same frequency and severity, except for the direction of the critical variable to be investigated, i.e. the sign of OTR in general and the contraversive tilt of SVV in particular. Therefore, we compared the patients with contraversive tilt of SVV with a second group of eight patients with cerebellar lesions admitted in the same period with an *ipsiversive* tilt of static SVV. Both groups were comparable with respect to age, acuteness and size of lesion, frequency of OT, SD, head tilt and other ocular disturbances such as abnormalities in saccadic movements and nystagmus (Table 1). In the comparison group with ipsiversive tilts of the SVV, four patients had lesions of the left and four lesions of the right cerebellum. In a subgroup analysis of the sample of the 31 patients, we further investigated the lesions of patients with other components of OTR, such as OT and SD. However, due to the small number of patients in the subgroups we did not calculate a subtraction analysis.

Patients who were not alert or not cooperative, as well as patients with unilateral hyporesponsiveness in the calorics tests indicating a possible peripheral vestibular lesion, were excluded. Patients with diffuse cerebellar as well as additional brainstem lesions were also excluded. None of the patients had either sensory abnormalities of the trunk or sensory deficits due to spinal cord syndromes. The patients gave their informed consent to participate in the study in accordance with the Declaration of Helsinki. Clinical and demographical variables are shown in Table 1. An experienced neuro-otologist performed the neuro-otological and neuro-otological examinations including testing of horizontal and vertical saccadic eye movements, nystagmus by using Frenzel’s glasses, and head tilt by using a protractor in all patients.

**Subjective visual vertical**

Subjects sat in an upright position looking into a hemispheric dome at a distance of about 1 m. The surface of the dome was covered with a random pattern of coloured dots containing no
cues to gravitational orientation. Subjects had to adjust the target disk at the centre of the dome to the vertical. Static SVV was determined by means of seven adjustments from a random offset position with the hemispherical dome stationary under binocular viewing conditions. Under these conditions, the normal range (+2 SD) of the SVV is ±2.5° (Dichgans et al., 1991; Dieterich and Brandt, 1993a). A mean of more than ±2.5° of the seven measurements of the static SVV determined binocularly was considered a criterion of a pathological tilt of static SVV (Dieterich and Brandt, 1993a). Tilts of the SVV in this setup are not simply the sensory consequence of the OT, which has to be measured by a red glass directly in front of each eye (Bixenman and von Noorden, 1982; Dieterich and Brandt, 1993b); they are mainly related to the function of spatial perception. Spatial perception is dependent on otolith and somatosensory input, and in this setup with patients without relevant somatosensory deficits mainly a function of otolith input.

Fundus photographs

Fundus photographs for measurements of tonic OT as a sign of vestibular dysfunction were made using a scanning laser ophthalmoscope. OT, in degrees, was defined as the mean of four to six fundus photographs. The position of the eye in the roll plane was determined as the angle between a straight line through papilla and macula and the horizontal line. With this method, the normal eye position for both eyes is an exocycloptoria of 5° (Curthoys et al., 1991, Dieterich and Brandt, 1993a). The net tilt angle for each eye was calculated as difference between 5° (normal eye position) and the measured angle of the cyclorotation.

Skew deviation

Measurements of vertical divergence (hypertropia/hypotropia) of the eyes were determined with the head upright, first by red glass testing and second using vertical orientated prisms of increasing angles of refraction while viewing a target binocularly during gaze straight ahead.

Lesion analysis

Lesion analysis was done by established brain imaging lesion techniques (Rorden and Karnath, 2004). The lesions of all patients were documented by MRI or by CT. Of the 31 patients with cerebellar infarctions, MR scans were performed in 24 patients, CT scans in 7 patients. The MRI protocol used diffusion-weighted and T2-weighted fluid-attenuated inversion-recovery imaging. Scans were obtained on a 1.5T echo planar imaging capable system (Magnetom Vision, Siemens, Germany). The fluid-attenuated inversion-recovery sequence was acquired with 19 axial slices (slice thickness 5 mm) with an interslice gap of 1 mm, a field of view of 175 × 230 mm2; a repetition time of 9000 ms and an echo time of 108 ms. Diffusion-weighted was performed with a single-shot echo planar imaging spin echo sequence (repetition time 5000 ms, echo time 137 ms, field of view 256 × 256 mm2; matrix 64 × 64 pixels; slice thickness 5 mm, gap 1 mm). MRI lesions were defined on fluid-attenuated inversion-recovery sequence and verified by diffusion-weighted sequence. To fit the canonical anterior commissure–posterior commissure orientation of the MR scans, the CT imaging protocol used the line drawn between the occiput and the lower margin of the orbita to orient the scans in each individual. CT scanning (Picker PQ 5000) was performed with a slice thickness of 3 mm infratentorial and 5 mm supratentorial. The initial scanning was optionally repeated during the following days until a firm diagnosis could be made and the infarcted area became clearly demarcated. These late scans were used in the present study to avoid possible artefacts due to edema or intracranial pressure. Furthermore, every lesion mapping plot was carefully examined for possible brain edema, which is also visible in the MRI/CT scan and might distort the lesion mapping.

The median time between lesion and the MRI used for the present analysis was 3 days (range 1–14 days); the median time between lesion and the CT scans 3 days (range 1–24 days). Using MRicro software (www.mricro.com) lesions were mapped onto slices of a T1-weighted template MRI scan from the Montreal Neurological Institute (MNI) (www.bic.mni.mcgill.ca/cgi/icbm_view). This template is approximately oriented to match Talairach space (Talairach and Tournoux, 1988). Lesions were mapped onto the slices that correspond to z-coordinates −55, −49, −43, −37, −31, −25, −19 and −13 mm in Talairach coordinates.

Results

Clinical data

Twenty-three (74%) of the 31 patients with acute unilateral cerebellar infarction presented with a contraversive tilt of SVV (binocular median SVV deviation 8.7°; range 3.5–15.0°), whereas only eight patients (26%) showed an ipsiversive tilt of SVV (binocular median SVV deviation 4.8°, range 3.3–19.8°). Thirteen patients with contraversive tilts of SVV had an OT (median net tilt angle of the OT of the right eyes: 6°, range 2–23°, and of the left eyes: 10°, range 2–13°) and four with ipsiversive tilts (median net tilt angle of the OT of the right eyes: 6°, range 2–11°; left eyes: 7°, range 3–11°) Thus, 57% of the patients with contraversive and 50% of the patients with ipsiversive tilt of SVV showed OT. SD was found in only six patients with contraversive tilts (median deviation 3.9°, range 2–11°) and two patients with ipsiversive tilts (2 and 8°). All eight patients with SD also showed the other signs of OTR, i.e. a complete OTR was only seen in a total of 8 of the 31 patients (26%). Of the eight patients with ipsiversive tilts of SVV, four patients (50%) showed a head tilt to the ipsiversive side (median 10°, range 5–20°), whereas in the group with contraversive tilts of SVV a head tilt to the contraversive side was demonstrated by eight patients (35%) (median 10°, range 7–20°). The frequencies of other ocular disturbances such as nystagmus, and abnormal saccadic eye movements are shown in Table 1.

Lesion analysis

In both groups lesions included the uvula, the pyramid of the vermis, the tonsil, the flocculus, the dentate nucleus, as well as the cerebellar peduncles and hemispheres (Table 2). Figure 1A and B illustrates lesion density plots for each of the two groups. To identify the structures that are specifically damaged in patients with contraversive and ipsiversive tilts of SVV, we subtracted the superimposed
lesion of the ‘comparison’ group, i.e. the group with ipsiversive tilts, from the overlap image of the group with contraversive tilts and vice versa. This revealed a percentage overlay plot, which codes the relative incidence of damage specific to patients with contraversive and ipsiversive tilts of SVV. It creates an image that highlights regions that are frequently damaged in patients with contraversive tilts of SVV as well as regions mainly damaged in patients with ipsiversive tilts of SVV. Figure 1C illustrates that the area specifically related to contraversive tilts of SVV is the dentate nucleus. On the other hand, no damaged lesion highly associated with ipsiversive tilts of SVV could

Table 2  Number and percentage (in brackets) of the cerebellar lesions in patients with ipsiversive or contraversive tilts of the SVV

<table>
<thead>
<tr>
<th>Tilts of the SVV [N (%)]</th>
<th>Middle cerebellar peduncle</th>
<th>Dentate nucleus</th>
<th>Pyramid of vermis</th>
<th>Uvula</th>
<th>Tonsil</th>
<th>Flocculus</th>
<th>Nodulus</th>
<th>Biventer lobule</th>
<th>Inferior semilunar lobule</th>
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<tr>
<td>Ipsiversive 8 patients</td>
<td>6 (75)</td>
<td>3 (38)</td>
<td>3 (38)</td>
<td>3 (38)</td>
<td>5 (63)</td>
<td>3 (38)</td>
<td>0</td>
<td>5 (63)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Contraversive 23 patients</td>
<td>12 (52)</td>
<td>21 (91)</td>
<td>9 (35)</td>
<td>9 (35)</td>
<td>16 (70)</td>
<td>1 (4)</td>
<td>2 (9)</td>
<td>7 (30)</td>
<td>3 (13)</td>
</tr>
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</table>

Fig. 1  (A) Overlay lesion plot of the patients with contralesional tilt of the SVV (n = 23). The number of overlapping lesions is illustrated by different colours coding increasing frequencies from violet (n = 1) to red (n = 23). (B) Overlay lesion plot of the comparison group with ipsilesional tilt of the SVV (n = 8). Number of overlapping lesions is illustrated by different colours coding increasing frequencies from violet (n = 1) to red (n = 8). (C) Overlay plot of the subtracted superimposed lesions of the patients with contralesional tilt of the SVV minus the comparison group and vice versa. The percentage of overlapping lesions of the group with contralesional tilt of the SVV after subtraction of the comparison group is illustrated by five different colours coding increasing frequencies from dark red (difference 1–20%) to white–yellow (difference 81–100%). Each colour represents 20% increments. The colours from dark blue (difference –1 to –20%) to light blue (difference –81 to –100%) indicate regions damaged more frequently in the comparison group than in patients with contralesional tilt of the SVV. Talairach z-coordinates of each transverse slice are given (Talairach and Tournoux, 1988). The figure illustrates that the anatomical area related to contraversive tilts of the SVV is the dentate nucleus.
be identified. The centre of the maximum overlap to contraversive tilts of SVV was located at $x = C0_{13}, y = C0_{55}$ and $z = C0_{37}$, corresponding to the coordinates of the dentate nucleus described by Dimitrova et al. (2002). We found that this area was 63% more frequently affected in patients with contraversive tilts of SVV than in the patient group with ipsiversive tilts of SVV ($\chi^2 = 9.828; P = 0.006$). All but 2 of the 23 patients with contraversive tilts of SVV had a lesion involving the dentate nucleus according to the coordinates described by Dimitrova et al. (2002). Furthermore, using a 3D MRI atlas of the dentate/interposed nucleus based on a probabilistic approach, the $z$-value does match the maximum region of interest overlap, whereas $x$- and $y$-values do meet the extensions in MNI space of the second highest overlap (Dimitrova et al., 2006). In contrast, we found the dentate nucleus only partly affected in three subjects from the comparision group. However, none of the lesions from the comparison group affected the centre of the maximum overlap (see above) in the patients with contraversive tilt of SVV (Fig. 1B).

If we consider the subgroup of the 13 patients with contraversive OT, we obtained a similar lesion distribution, which showed the dentate nucleus as the structure with the maximum overlap at very similar coordinates $x = -13, y = -54$ and $z = -37$. Eleven patients had these lesions of the dentate nucleus, whereas in the four patients with ipsiversive OT the cerebellar hemispheres were more affected ($\chi^2 = 9.590; P = 0.006$) (Fig. 2A and B). Slightly different results were obtained in the subgroup of the six patients with contraversive SD, who not only had a maximum overlap at the dentate nucleus ($x = -12, y = -53, z = -37$), but also at the tonsil ($x = -6, y = -48, z = -43$). However, the tonsil was also affected in one of the two patients with ipsiversive SD (Fig. 3A and B).

To clarify the role of the dentate nucleus with respect to head tilt, lesions of the patients with contraversive tilt of the SVV and contraversive head tilt were compared with those of patients with contraversive tilt of SVV without head tilt. The data demonstrated that the dentate nucleus was involved in both groups ($\chi^2 = 0.003; P = 0.955$) (Fig. 4A and B).

**Discussion**

Our data of patients with cerebellar infarctions presenting with a vestibular tone imbalance suggest that the dentate nucleus might be a critical anatomical structure of a network within the cerebellum involved in the processing of vestibular information for the roll plane. It is affected in patients with contraversive tilts of SVV, OT, SD and head tilt but is significantly less involved in patients with unilateral cerebellar lesions presenting with ipsiversive signs of OTR. In addition, these data revealed that contraversive SVV tilts were more frequent (74%) and were associated with lesions including the middle cerebellar peduncle, the pyramid of the vermis, the tonsil, the flocculus, the nodulus, the biventer lobule, the inferior semilunar lobule and the uvula. Ipsiversive tilts of the SVV were less frequent (26%) and were associated with lesions of the biventer lobule, and the inferior semilunar lobule apart from the middle cerebellar peduncle, the pyramid of the vermis, the tonsil, the flocculus and the uvula. With respect to the components of OTR, i.e. OT and SD, similar lesion distributions were obtained. Thus, apart from

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**Fig. 2** (A) Overlay lesion plot of the patients with contralesional OT ($n = 13$). The number of overlapping lesions is illustrated by different colours coding for increasing frequencies from violet ($n = 1$) to red ($n = 13$). The lesion is centred on the dentate nucleus. (B) Overlay lesion plot of the comparison group with ipsilesional OT ($n = 4$). The number of overlapping lesions is illustrated by different colours coding for increasing frequencies from violet ($n = 1$) to red ($n = 4$). Major overlaps of the lesions are located on the biventer lobule and the inferior semilunar lobule.
commonly affected structures, the differentiation discloses parts of the cerebellar hemispheres such as the biventer and inferior semilunar lobule for ipsiversive signs and the dentate nucleus for contraversive signs.

In the normal upright position in the roll plane, the SVV is aligned with the gravitational vertical and the axes of the eyes and head are horizontal and directed straight ahead. Unilateral lesion or stimulation of the utricular or vertical semicircular canal paths leads to an imbalance in the vestibular tone of the roll plane, resulting either in a complete OTR or in single components (Halmagyi et al., 1979; Vibert et al., 1996, 1999). These components were found with decreasing frequencies in brainstem lesions: the most frequent were SVV tilts (94%), followed by OT (83%) and SD (31%) (Dieterich and Brandt, 1993a; Brandt and Dieterich, 1994).
With regard to the cerebellar structures associated with OTR, there are a few reports that indicate that damage of the vermis or the hemispheres is involved in the pathogenesis of SD (Wong and Sharpe, 2005). These authors examined five patients with cerebellar lesions of the vermis or the cerebellar hemispheres, all of whom had SD and an asymmetric static torsional VOR. Thus, the authors conclude that cerebellar SD is due to an imbalance of the utricular-ocular reflex mediated by an asymmetry between the eyes or in direction of the static torsional VOR. However, to our knowledge there are no systematic anatomical studies examining cerebellar lesions in humans with respect to the signs of the VOR in the roll plane. Thus, the question arises as to which cerebellar structures are involved in the processing of vestibular signals needed for perception of verticality. One case study of two patients with contraversive partial OTR suggested that both, lesions of the nodulus and uvula, may lead to a contraversive OTR (Mossmann and Halmagyi, 1997). One patient had a left caudal cerebellar haemorrhage involving the left side of the nodulus and the other patient had an infarction of the medial branch of the left posterior inferior cerebellar artery that involved the tonsil, the uvula, the biventer lobules and the left side of the inferior vermis including the left side of the nodulus. Here, OTR seemed to be due to an interruption of the inhibitory projections from the lesioned nodulus to the graviceptive neurons in the ipsilateral VN. Another case study (Min et al., 1999) that reported on two patients with contraversive incomplete OTR, one with cerebellar haemorrhage involving the nodulus and the dentate nucleus, the other with an infarct involving the nodulus, uvula and VN, supported previous results (Mossmann and Halmagyi, 1997). Other recently published data on two patients with ipsiversive OTR caused by an anterior inferior cerebellar artery infarction, suggested that damage to the inner ear or the root entry zone of the eighth nerve plays a role in mechanisms of ipsiversive OTR (Lee et al., 2005). Indeed, lesions of the eighth nerve (Halmagyi and Curthoys, 1988; Schulz et al., 1999) as well as lesions of the VN and the root entry zone were shown to cause ipsiversive tilts (Dieterich and Brandt, 1993a), whereas lesions of the vestibular pathways of the ponto-mesencephalic brainstem above the vestibular nuclei, such as the medial longitudinal fasciculus and interstitial nucleus of Cajal, cause contraversive tilts (Dieterich and Brandt, 1992, 1993a; Brandt and Dieterich, 1994). Thus, due to the lack of systematic anatomical studies in the human cerebellum, the cerebellar mechanisms that lead to contra- and ipsiversive tilts, such as OTR in general and tilt of the SVV in particular, are far from clear. Our current data shed some light on this issue by showing an association between lesions of the dentate nucleus and contraversive signs of OTR.

The uvula, nodulus and flocculus have extensive connections to the vestibular nuclei and are parts of a network processing vestibular signals, the ‘vestibulo-cerebellum’. In the present study, two patients with contraversive signs of OTR (Table 2) had involvement of large parts of the nodulus: in one of the patients the dentate nucleus was intact, whereas the other one also had a lesion affecting the dentate nucleus. Thus, in accordance with the results of Mossmann and Halmagyi (1997) a lesion of the nodulus sparing the dentate nucleus also led to contraversive signs of OTR. With respect to the role of the flocculus, another important part of the ‘vestibulo-cerebellum’, the lesion in two patients with ipsiversive signs of OTR did not affect the dentate nucleus. Thus, the hypothesis of previous animal studies in rabbits (Barmack, 2003) that lesions to the uvula, nodulus and flocculus influence the processing of vestibular information might also be true for humans. But also deep cerebellar nuclei such as the fastigial and the dentate nucleus (i.e. lateral cerebellar nucleus) are connected to the vestibular nuclei in animal studies (Brodal and Hoivik, 1964; Dickman and Fang, 1996; Büttner et al., 1999; Delfini et al., 2000). Electrophysiological studies in the rabbit indicate that the dentate nucleus represents one of the ‘relay’ sites for vestibular signals (Highstein, 1971, 1973). Corresponding results come from a study showing that in rabbits, neurons of the lateral cerebellar nuclei responded to head and body tilts along the longitudinal axes, indicating that these receptors should be evoked by signals from the otoliths (Favilla et al., 1978). Other animal studies in rats investigated the effect of the dentate nucleus on balance and spatial orientation and found that rats with midline lesions comprising the vermis and fastigial nucleus, as well as rats with unilateral lesions involving the dentate nucleus and cerebellar hemispheres, showed a disturbance of equilibrium (Joyal et al., 1996, 2001).

However, there are no studies available for unilateral lesions of the dentate nucleus in animals and only one in humans. In fact, there is one older case report on the stimulation of the dentate nucleus using stereotactically inserted electrodes in two patients, one having bilateral tremor, the other exhibiting athetosis of the arms (Nashold et al., 1969). Here, stimulation of the dentate nucleus of one side resulted in ipsiversive conjugate eye movements as well as ipsiversive head deviation, whereas coagulation of the dentate nucleus resulted in contraversive tilting of the head and eye deviation. This report of a patient with a unilateral dentate nucleus lesion fits nicely with our current data. Therefore, we suggest that the dentate nucleus seems to play a crucial role in the otolith-based perception of verticality, and that a unilateral lesion of the dentate nucleus may cause a disturbed internal representation of verticality of eyes, head and body. Since the deep cerebellar nuclei provide the major output station (Ruigrok et al., 1996; Mauk, 1997) and animal studies indicate that the dentate nucleus presents an input station for vestibular signals (Highstein, 1971, 1973), we assume that the dentate nucleus (lateral cerebellar nucleus) represents one major station for the processing of vestibular signals in the human.
A lesion of the input site of vestibular signals could, on the one hand, nicely explain the dysfunction of the perception of verticality, measured by tilts of the SVV, as well as lesion-induced vestibular ocular motor consequences such as OT. On the other hand, head tilt, OT and SD could also be derived from a loss of regular motor innervation due to a lesion of the (motor) output station. However, a dysfunction of the motor output station would most probably not cause perceptual tilts but only SD and OT, since ocular motor innervation only corrects for the differences in pulling directions and strengths of the ocular muscles when the position of the eye is changed. Furthermore, the role of the motor system represented by head tilt was addressed in a lesion analysis of the patients with contralesional tilts of the SVV with and without head tilt. Since both groups showed similar anatomical results (Fig. 4A and B), it seems unlikely that the motor system has a dominant influence.

Nevertheless, considering that two of our patients with an unaffected dentate nucleus also showed a contraversive tilt of SVV and that none of our patients had an isolated lesion of the dentate nucleus, it appears that other cerebellar structures are also involved in the perception of verticality. Therefore, we rather favour the hypothesis that the dentate nucleus is a crucial cerebellar structure in a network with visual, vestibular and somato-sensory input (Fig. 5A). In view of our present data, we suggest that the mechanisms postulated by Mossman and Halmagyi (1997), i.e. that perception of verticality is exclusively under inhibitory control of the ipsiversive nodulus, should be modified in the sense that the loss of inhibition not only from the lesioned nodulus and the uvula but also from the lesioned dentate nucleus as processing station leads to an increase in tonic resting activity in the ipsilesional vestibular nuclear complex (VN) and thus to a contralesional tilt of the SVV. (C) Lesions of the cerebellum excluding dentate nucleus, nodulus and uvula lead to an excessive inhibitory activity of the dentate nucleus [-] due to the loss of inhibitory efferents from the cerebellar lobule and thus to a decrease of tonic resting activity in the vestibular nuclei and consequently to an ipsiversive tilt of the SVV.

Fig. 5 Schematic explanation of tilt of the SVV due to lesions of the dentate nucleus, nodulus, uvula or the cerebellar hemispheres. (A) Normal circuit with inhibitory [-] projections from the cerebellar lobule and the nodulus/uvula to the dentate nucleus and from the dentate nucleus to the VN. An additional inhibitory pathway goes from the nodulus directly to the VN. (B) Lesions of one dentate nucleus (1), or nodulus/uvula (2) or both (1 + 2) leading to an increase in tonic resting activity in the ipsilesional vestibular nuclear complex (VN) due to loss of inhibition [equivalent to an excitation (+)] and thus to a contralesional tilt of the SVV. (C) Lesions of the cerebellum excluding dentate nucleus, nodulus and uvula lead to an excessive inhibitory activity of the dentate nucleus [-] due to the loss of inhibitory efferents from the cerebellar lobule and thus to a decrease of tonic resting activity in the vestibular nuclei and consequently to an ipsiversive tilt of the SVV.
Analysis of SD indicated an involvement of the tonsil. Previous case studies described SD in lesions of the nodus, the vermis or the cerebellar hemispheres (Mossmann and Halmagyi, 1997; Wong and Sharpe, 2005). However, since clinical reports of unilateral SD in patients with purely cerebellar lesions are rare and the present sample of six patients was small, further investigations have to be done to answer the question of whether the tonsil may be a key station in SD or not.

While otolith information is important for determining head orientation, neck and trunk proprioception might also be relevant. In fact, the results of Yardley (1990) suggested that proprioception might play a role in the perception of the SVV. Lesion comparison of the patients with contraluminal tilt of SVV and head tilt and patients with contralesional tilt of the SVV without head tilt demonstrated that the dentate nucleus was involved in both groups (Fig. 4A and B). Thus, the dentate nucleus is the crucial anatomical structure for the otolith-based perception of verticality, which may be associated with head tilt, but it is not the head tilt—as a sign of motor or proprioception performance—which is related to the dentate nucleus. We cannot definitely exclude the possibility that other sensory input, e.g. from the somatosensory system, might mediate non-postural upright (Karnath et al., 2000). Experimental observations indicated that somatosensory information for the perception of body posture and spatial orientation might have only modulatory character. Proprioceptive input of the lower extremities was found to only indirectly affect the perception and control of posture by implementing or modulating the output of the truncal graviceptors (Mittelstaedt, 1992, 1998). In addition, one patient with a complete left-sided sensory loss due to a thalamic lesion did not show any difficulties in the veridical perception of postural upright (Karnath et al., 2000). These data suggest that the perception of orientation in space is dependent on several sensory inputs, of which the otolith system seems to play a more important role than the proprioceptive system.

In conclusion, the sample of patients with unilateral cerebellar infarcts that presented with contra- and ipsiversive signs of OTR gave evidence that the dentate nucleus is an important anatomical structure—probably both a relay and a processing station—within a network significantly involved in the perception of spatial orientation of eyes, head and body.

However, the limitations of the present study should be kept in mind, since structural MRI and CT scans might not necessarily show the full functional extent of a lesion. Areas, which appear structurally intact in anatomical scans, may not necessarily be functioning normally due to an abnormal perfusion. Therefore, perfusion-weighted imaging, which measures the amount and latency of blood flow in certain regions, provides a promising new tool to address these issues in future studies. Another limitation might be the limited spatial resolution of the MNI template used, and the difficulty of clearly identifying the border between the interposed and the dentate nucleus. However, even Dimitrova et al. (2006) admit that their cerebellar atlas mainly describes the localization of the dentate nucleus due to the small size of the interposed nuclei. Indeed, our coordinates match the x, y, z extensions described by Dimitrova et al. (2002, 2006), thus supporting the conclusion that the maximum anatomical overlap in patients with contraversive signs of OTR mainly represents the dentate nucleus.

The question of whether the dentate nucleus might also be involved in the processing of vestibular signals, as opposed to merely transmitting signals, cannot be conclusively answered by the present study. However, since the dentate nucleus seems to be an anatomical key structure and isolated lesion or stimulation of the dentate nucleus cause signs of OTR (Nashold et al., 1969), we assume that the function of the dentate nucleus is not only restricted to transmission but also includes processing of vestibular signals. Furthermore, higher cognitive function of the cerebellum as demonstrated in spatial attention tasks support the hypothesis that the cerebellum does not only present a passive contributor to perceptual spatial processes (Townsend et al., 1999; Golla et al., 2005). Therefore, we suggest that the cerebellum in general and the dentate nucleus in particular is also involved in an active cognitive process of spatial perception.

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References


