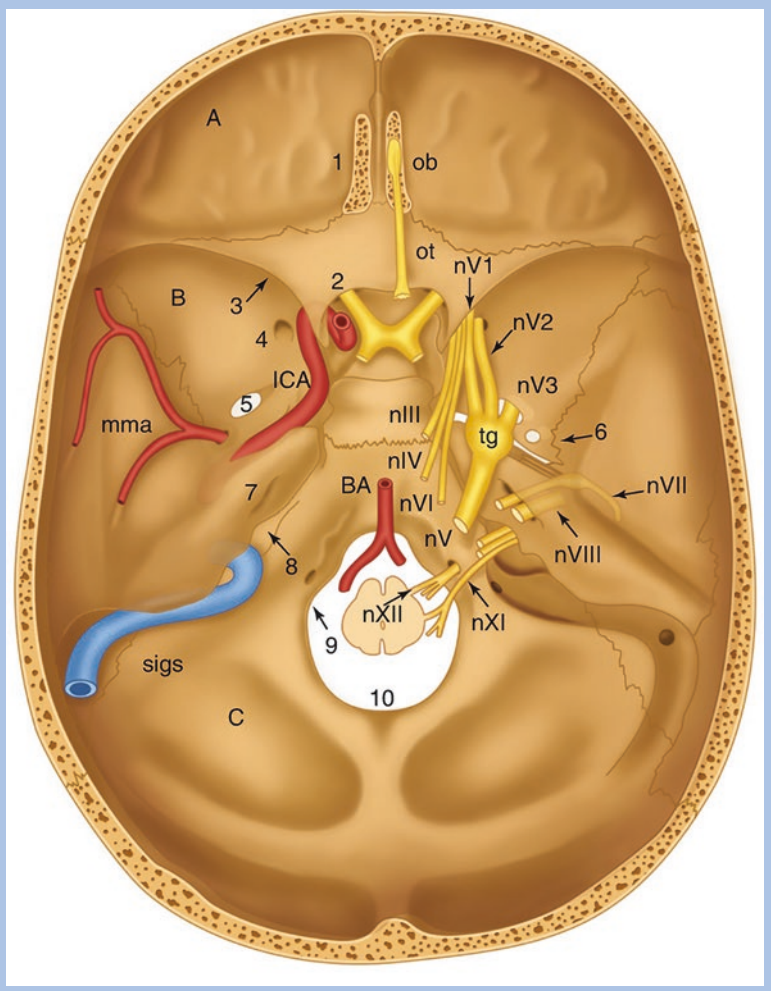
The Cranial Nerves

Hans J. ten Donkelaar, David Kachlík, Johannes R. M. Cruysberg, Ton van der Vliet, and Peter van Domburg



Skull base with cranial nerves

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Contents

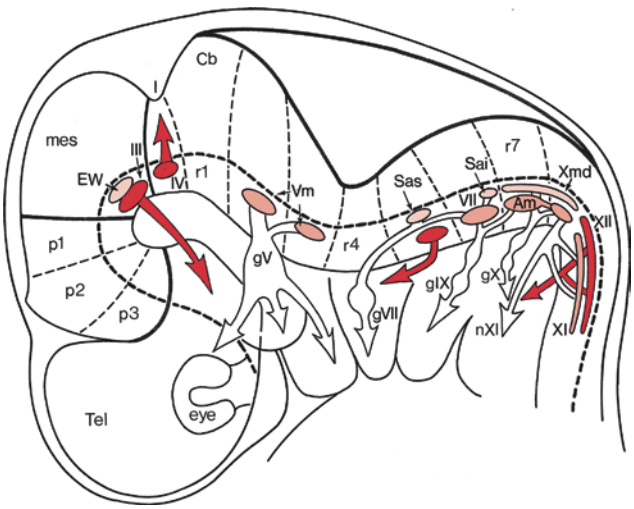
6.1 Introduction

With the exception of the olfactory and optic nerves, all cranial nerves enter or leave the brain stem. Three of the cranial nerves are purely sensory (I, II and VIII), five are motor (III, IV, VI, XI and XII), and the remaining nerves (V, VII, IX and X) are mixed. The olfactory nerve will be discussed in ▶ Chap. 14, the optic nerve in ▶ Chap. 8 and the cochlear nerve in ▶ Chap. 7. The nuclei of the cranial nerves are arranged in an orderly, more or less columnar fashion in the brain stem: motor nuclei, somatomotor, branchiomotor and visceromotor (parasympathetic), derived from the basal plate, are located medially, whereas sensory nuclei, somatosensory, visceral sensory and vestibulocochlear, derived from the alar plate, are found lateral to the sulcus limitans. Recent evidence in mouse embryos showed that branchiomotor and visceromotor neurons are presented next to the floor plate and later migrate dorsolaterally to their final position (Puelles et al. 2019). The cranial nerves innervate structures in the head and neck as well as visceral organs in the thorax and abdomen. The cranial nerves control eye movements, mastication, vocalization, facial expression, respiration, heart rate and digestion. One or several of the cranial nerves are often involved in lesions of the brain stem, of which the location can usually be determined if the topographical anatomy of the cranial nerves and their nuclei is known (Brodal 1981; Duvernoy 1995; Leblanc 1995). Several examples are shown in ▶ Clinical Cases 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 6.10, 6.11, 6.12, 6.13, 6.14, 6.15, and 6.16. Following a few notes on the development of the brain stem and some developmental disorders (▶ Sect. 6.2), the ocular motor nerves (▶ Sect. 6.3), eye movements (▶ Sect. 6.4), the trigeminal nerve (▶ Sect. 6.5), the facial nerve (▶ Sect. 6.6), the gustatory system (▶ Sect. 6.7), the vestibular nerve and vestibular control (▶ Sect. 6.8) and the last four cranial nerves (▶ Sects. 6.9 and 6.10) will be discussed. The cochlear nerve is discussed in ▶ Chap. 7. For the terminology, the English terms of the *Terminologia Neuroanatomica* (TNA 2017; see ten Donkelaar et al. 2017, 2018) are used.

6.2 A Few Notes on the Development of the Brain Stem

At least during development, the brain stem is segmentally organized. The midbrain is composed of 2 temporarily present segments known as the **mesomeres**, whereas the hindbrain is composed of 11, also temporarily present, **rhombomeres**. In between, the isthmic neuromere (or rhombomere 0) is found (Watson et al. 2017, 2019). The motor nuclei of the extraocular muscles arise from mesomere 1 (the oculomotor nucleus), rhombomere 0, the isthmic neuromere (the trochlear nucleus) and rhombomere 5 (the abducens nucleus). The motor nuclei of the cranial nerves, innervating the branchial or pharyngeal arch musculature, arise from the second, fourth, sixth and seventh-eleventh rhombomeres (◘ Fig. 6.1). The neural crest, flanking the developing rhombencephalon, makes important contributions to the pharyngeal arches (ten Donkelaar et al. 2014b). A great number of genes are involved in the proper development of the brain stem (Cordes 2001; Pasqualetti and Rijli 2001; Guthrie 2007). The isthmus organizer regulates the early development of the mesencephalon and of the rostral part of the rhombencephalon (Wurst and Bally-Cuif 2001; ten Donkelaar et al. 2014a). Mutations of genes involved in this process, such as *Otx2*, *En1* and *En2*, result in extensive defects of the midbrain, the cerebellum and the pontine tegmentum.

Rhombomeres are thought to acquire their individual identities under the influence of *Hox* genes that are expressed in overlapping or nested domains (Lumsden and Krumlauf 1996). *Hox* gene expression precedes rhombomere foundation but becomes progressively sharpened such that the borders of the expression domains coincide with the emerging rhombomeric boundaries. Rhombomeres 2 to 6 can be recognized as overt bulges, represented by constrictions in the embryonic hindbrain (see Müller and O'Rahilly 1997; ten



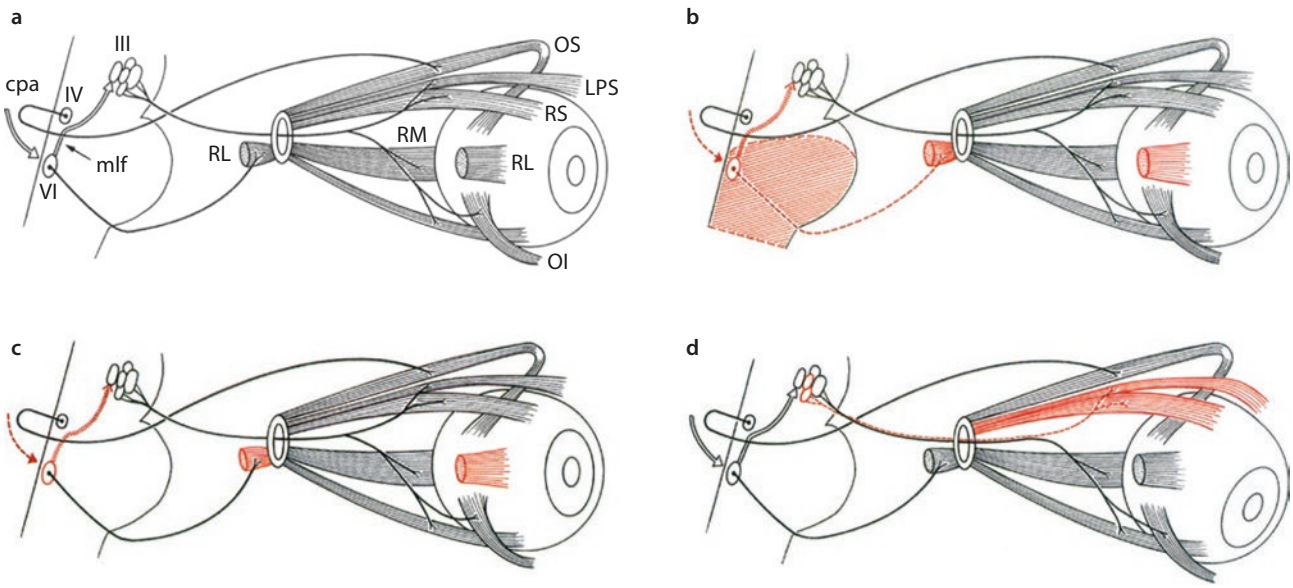
◘ **Fig. 6.1** The relation of the human cranial nerve nuclei to the rhombomeres. Somatomotor nuclei are shown in *red*, branchiomotor nuclei in *medium red* and parasympathetic nuclei in *light red*. Am ambiguus nucleus (motor nucleus of IXth and Xth nerves), Cb cerebellum, EW nucleus of Edinger-Westphal, gV, gVII, gIX, gX cranial nerve ganglia, I isthmus, mes mesencephalon, nXI accessory nerve, p1–p3 diencephalic prosomeres, r1–r7 rhombomeres, Sai, Sas inferior and superior salivatory nuclei, Tel telencephalon, III, IV, Vm, VI, VII, IX, XII cranial nerve nuclei and nerves (*arrows*), Xmd dorsal nucleus of vagus nerve. (After Puelles López et al. 2008; from ten Donkelaar et al. 2014a)

Donkelaar et al. 2014c). The caudal hindbrain was first subdivided into two rhombomeres, r7 and r8. Fate mapping and differential *Hox* gene expression in the avian (Marín et al. 2008) and more recently the mouse medulla oblongata (Tomás-Roca et al. 2016) suggested a further subdivision into rhombomeres r7 to r11, described as pseudorhombomeres or cryptorhombomeres. Currently, the hindbrain is divided into the **rostral hindbrain**, composed of the isthmic rhombomere and rhombomeres 2–6, and the **caudal hindbrain,** composed of the rhombomeres 7 to 11 (Watson et al. 2019; see ▶ Chap. 1).

Available human data suggest that the pattern of *HOX* gene expression in the rhombomeres and pharyngeal arches is comparable to that of *Hox* genes in mice (Vieille-Grosjean et al. 1997). In mice, spontaneous and targeted (knockout) mutations in these genes result in specific, rhombomere-restricted disruptions in the development of the motor nuclei of the cranial nerves. In *Hoxa1* knockout mice, rhombomeres 3–6 are not formed (Carpenter et al. 1993; Gavalas et al. 1998, 2003; Rossel and Capecchi 1999). For data on the human homologue *HOXA1* (Tischfield et al. 2005; Engle 2006, 2007, see ◘ Fig. 6.2). Such segmental shifts in the brain stem or ***rhombomeropathies*** have been described for the *HOXA1* gene (Tischfield et al. 2005; Engle 2006, 2007; Bosley et al. 2007, 2008).

Many other genes play a role in the differentiation, migration, axon formation and guidance of (moto)neurons (for reviews see Cordes 2001; Guthrie 2007; ten Donkelaar et al. 2014a). **Facial branchiomotor neurons** arise in rhombomere 4 (r4) and migrate through r5 to r6 (passing the abducens nucleus), where they form the facial motor nucleus. In humans, this caudalward migration continues until far in the fetal period. The passing of the abducens nucleus may explain the combination of facial and abducens motoneuron loss seen in cases of the Möbius syndrome and related disorders. **Trigeminal motoneurons** remain within their rhombomeres of origin and move dorsolaterally to the point of exit of the trigeminal nerve in the dorsal half of r2/r3.

Developmental anomalies of one or more cranial nerves, with primary or secondary dysinnervation, may lead to congenital, nonprogressive, sporadic or familial abnormalities of cranial musculature, currently grouped as ***congenital cranial dysinnervation disorders*** (***CCDDs***; Gutowski et al. 2003; Heidary et al. 2012). Maldevelopment of oculomotor and facial motor nuclei, in isolation or in combination, may result in various phenotypes (Engle 2002, 2006, 2007; Engle and Leigh 2002), characterized by abnormal eye, eyelid and/or facial movements. Three CCDDs are summarized in ◘ Fig. 6.2: the ***HOXA1 syndrome***, in which early motoneuron development is disrupted (Bosley et al. 2007, 2008); ***horizontal gaze palsy*** with ***progressive scoliosis***, in which there is aberrant axonal targeting to abducens motoneurons (Jen et al. 2002, 2004; Pieh et al. 2002; Sicotte et al. 2006); and ***congenital fibrosis*** of the ***extraocular muscles type 1***, in which there is aberrant axonal targeting to the extraocular muscles. Some other examples can be found in ▶ Clinical Case 6.1.



◘ **Fig. 6.2** The congenital cranial dysinnervation disorders. The extraocular muscles and their innervation are shown in **a** healthy individuals, **b** ***Bosley-Salih-Alorainyl Athabascan brainstem dysgenesis syndromes***, **c** ***horizontal gaze palsy with progressive scoliosis*** and **d** ***congenital fibrosis*** of the ***extraocular muscles type 1***. Aberrant or missing structures involved are shown in *red*. cpa crossed pontine axons; mlf medial longitudinal fascicle; LPS levator palpebrae superioris muscle; OI, OS inferior and superior oblique muscles; RL, RM, RS lateral, medial and superior rectus muscles; III, IV, VI oculomotor, trochlear and abducens nuclei. (After Engle 2006)

Clinical Case 6.1 Congenital Cranial Dysinnervation Disorders

Congenital cranial dysinnervation disorders **(*CCDDs*)** include congenital, nonprogressive, sporadic or familial abnormalities of, or the complete absence of, one or more cranial nerves with primary or secondary muscle dysinnervation (Gutowski et al. 2003; Engle 2007). They are characterized by abnormal eye, eyelid and/or facial movement (see **Case reports**).

Case report 1: A 7-year-old boy was referred because of frequent head turn to the left since infancy (Fig. 6.3a). The iris of the left eye showed a ***coloboma*** (Fig. 6.3b). Ocular motility showed abduction paralysis of the left eye (Fig. 6.3d) with narrowing of the palpebral fissure on attempted adduction (Fig. 6.3c). With his torticollis, the boy had binocular single vision. When the head was turned straight, he had horizontal diplopia caused by the abduction deficit of the left eye. Diagnosis: ***ocular torticollis*** caused by typical ***Duane retraction syndrome type I*** of the left eye. The narrowing of the palpebral fissure is caused by co-contraction of the left horizontal rectus muscles in gaze to the right. Duane syndrome type I is the most frequent CCDD. Duane syndrome occurs more often in left eyes than in right eyes and may be associated with other congenital anomalies such as iris coloboma.

Case report 2: A 31-year-old woman was referred by her internist for ocular examination because of her long history of congenital pituitary dysfunction and strabismus. The patient had no complaints of her vision. There was exotropia of the right eye with small angle of squint. Examination of ocular motility showed complete absence of horizontal ocular movements (Fig. 6.4) with retraction of the eyes on attempted adduction. Vertical eye movements were intact. The patient was diagnosed in the past as bilateral ***Duane retraction syndrome type III*** associated with congenital panhypopituitarism (Cruysberg et al. 1986). In the follow-up of 31 years, the ocular movement pattern had not changed. However, despite the absence of horizontal ocular movements, the extreme convergent strabismus of the first year of life had resolved spontaneously and resulted in mild divergent strabismus.

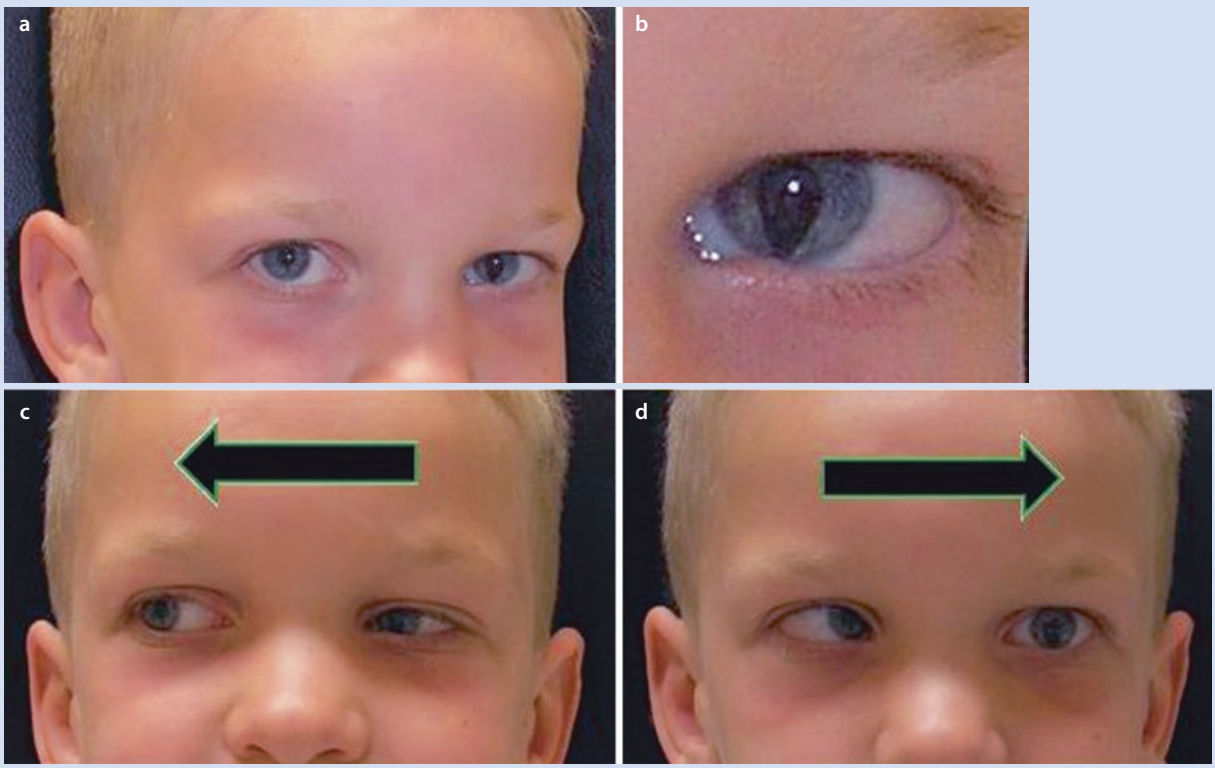


Fig. 6.3 ***Duane syndrome type I*****: a** Head turn to the left, with straight eyes; **b** iris coloboma of the left eye; **c** gaze to the right: note narrowing of palpebral fissure of the left eye; **d** gaze to the left: abduction paralysis of the left eye. (Courtesy Johannes Cruysberg, Nijmegen)

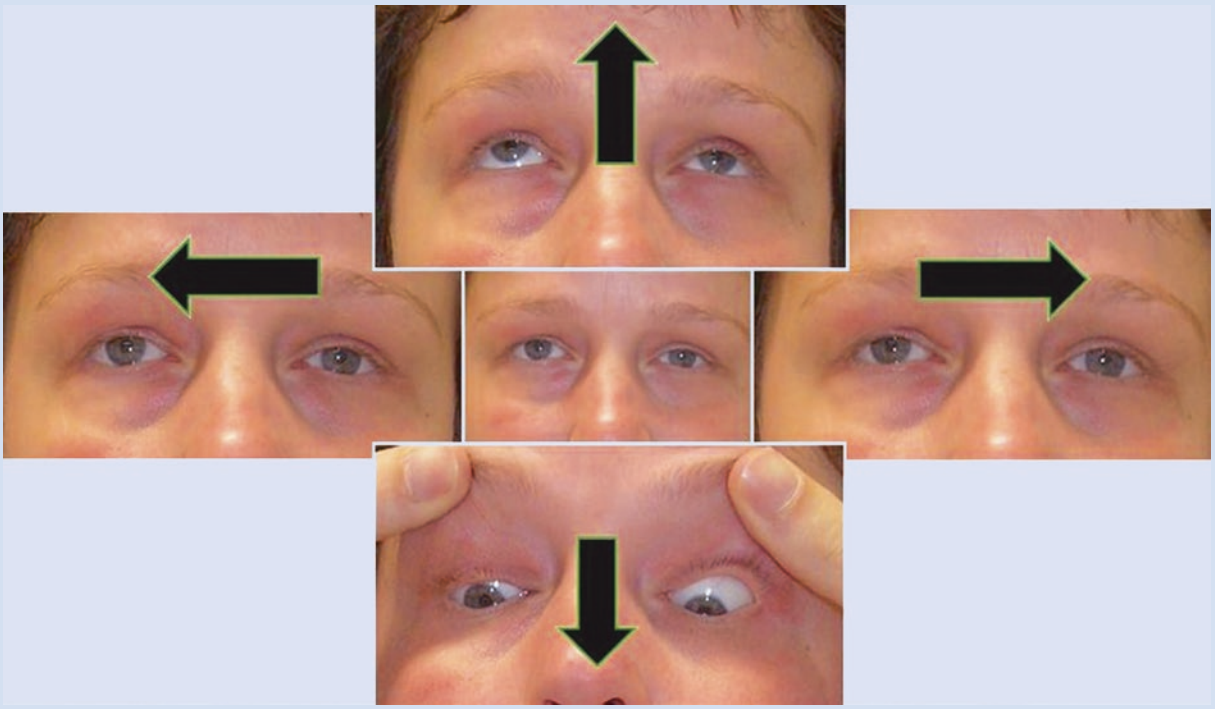


Fig. 6.4 ***Duane syndrome type III*:** Attempted gaze in horizontal and vertical directions. Note that ocular movements are only possible in vertical direction. (Courtesy Johannes Cruysberg, Nijmegen)

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6.3 The Oculomotor, Trochlear and Abducens Nerves

Apart from the lateral rectus and the superior oblique muscles, all extraocular muscles are innervated by the oculomotor nerve (Fig. 6.5). The superior oblique muscle is innervated by the trochlear nerve and the lateral rectus muscle by the abducens nerve. The exits of the ocular motor nerves from the brain stem can easily be visualized by MRI (Fig. 6.6a–c). The nuclei of the oculomotor, trochlear and abducens nerves are located close to the midline (Fig. 6.6d–f). The **oculomotor nerve** emerges from the midbrain in the interpeduncular fossa between the posterior cerebral and superior cerebellar arteries and enters the interpeduncular cistern. Then, it passes inferolateral to the posterior communi-

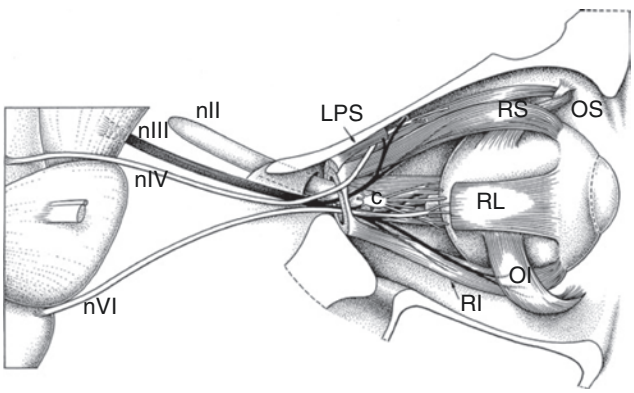


Fig. 6.5 The innervation of the extraocular muscles in a lateral view. c ciliary ganglion, LPS levator palpebrae superioris muscle, nII optic nerve, nIII oculomotor nerve, nIV trochlear nerve, nVI abducens nerve, OI, OS inferior and superior oblique muscles, RI, RL, RS inferior, lateral and superior rectus muscles. (After ten Donkelaar et al. 2007b)

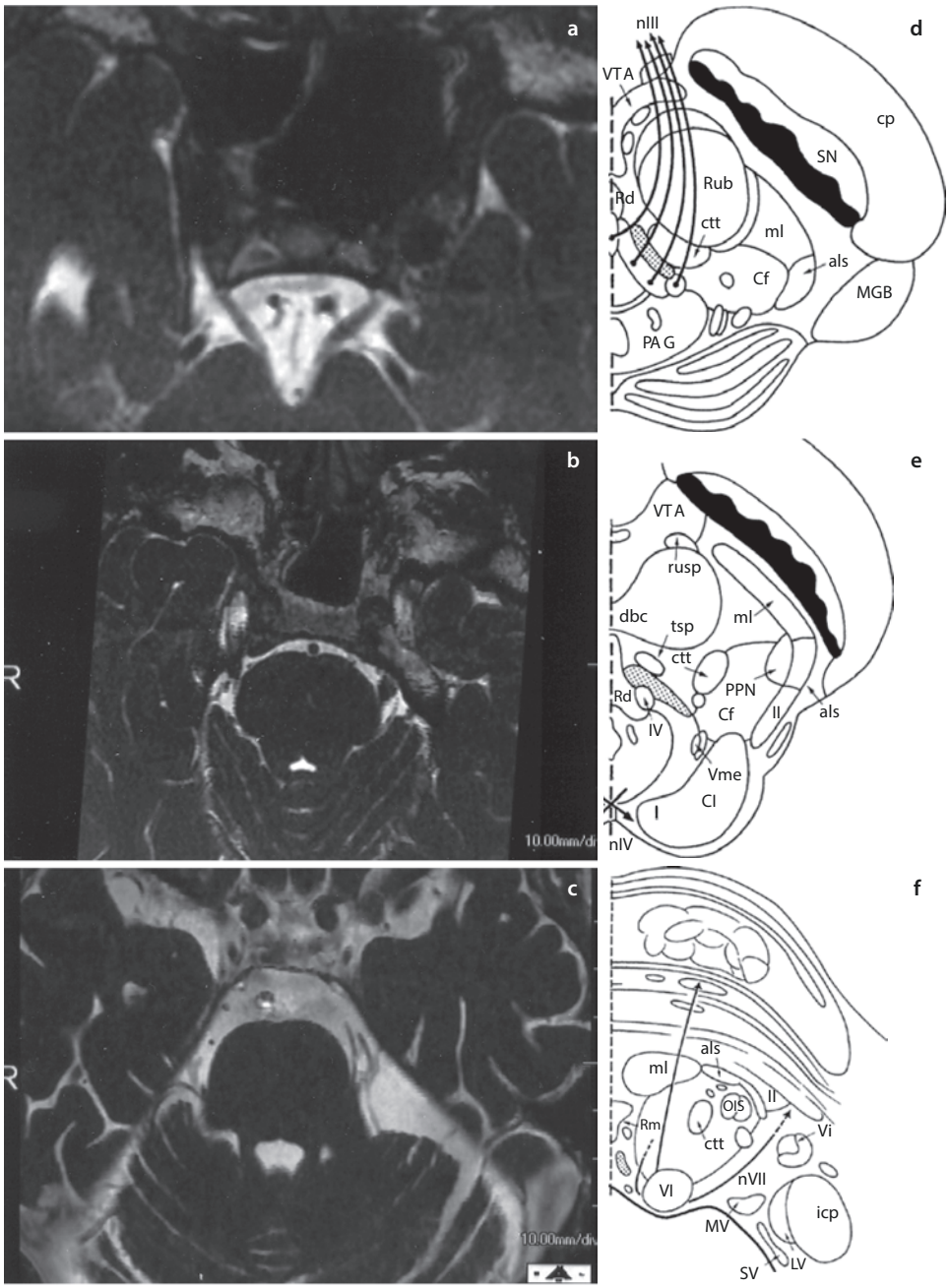


Fig. 6.6 **a–c** MRIs, showing the exits of the ocular motor nerves and corresponding horizontal sections through the human brain stem through the levels of **d** the oculomotor, **e** the trochlear (*IV*) and **f** the abducens (*VI*) nuclei. (After Duvernoy 1995). The oculomotor nerve (*nIII*) is formed by various components, median, main and more lateral the Edinger-Westphal nucleus. The trochlear nerve (*nIV*) decussates in the roof of the mesencephalon

cating artery, medial to the uncus, pierces the dura mater lateral to the posterior clinoid process, enters the dorsolateral wall of the cavernous sinus (see Fig. 6.9) and continues through the superior orbital fissure to bifurcate into superior and inferior branches. The **superior branch** ascends lateral to the optic nerve and innervates the levator palpebrae superioris and superior rectus muscles, whereas the **inferior branch** supplies the medial rectus, the inferior rectus and the inferior oblique muscles, and also contains the parasympathetic visceromotor branch to the ciliary ganglion. The **trochlear nerve** decussates in the isthmic part of the hindbrain within the superior medullary velum. It courses via the quadrigeminal and ambiens cisterns between the posterior cerebral and superior cerebellar arteries, lateral to the oculomotor nerve, to pierce the dura mater to enter the dorsolateral wall of the cavernous sinus, and passes through the superior orbital fissure to innervate the superior obliquus muscle. The **abducens nerve** emerges from the hindbrain in the medullopontine groove and courses ventrocranially within the prepontine cistern to pass through the dura mater into the fibro-osseous abducens nerve canal of Dorello. Then, it enters the mediobasal part of the cavernous sinus, where it lies

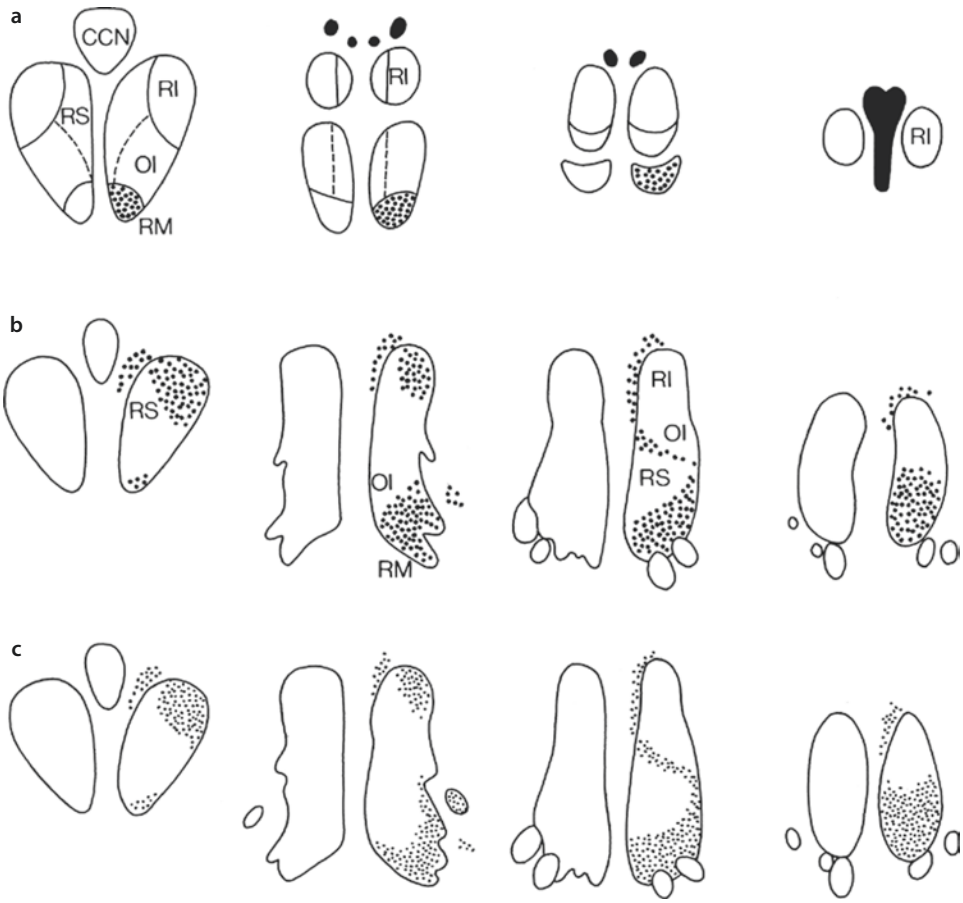


Fig. 6.7 The localization of extraocular muscles in, from left to right, the caudal, middle and rostral thirds and the rostral pole of the oculomotor complex of the rhesus monkey based on **a** experimental data by Warwick (1953) and **b** Büttner-Ennever and Akert (1981). In **a**, the Edinger-Westphal nucleus is shown in *black* and in **c**, the distribution of abducens internuclear terminals to the medial rectus motoneurons is shown. (After Büttner-Ennever and Akert 1981). CCN central caudal nucleus, OI inferior oblique motoneurons, RI, RM, RS inferior, medial and superior rectus motoneurons

adjacent to the internal carotid artery (see Fig. 6.9), and enters the orbit via the superior orbital fissure to innervate the lateral rectus muscle.

The **oculomotor nucleus**, situated in the periaqueductal grey from the level of the diencephalic-mesencephalic junction area to the lower level of the superior colliculus (Fig. 6.6d), innervates the levator palpebrae superioris muscle and all extraocular eye muscles except the superior oblique and lateral rectus muscle. In macaque monkeys, the oculomotor nucleus contains five subnuclei (Warwick 1953; Büttner-Ennever and Akert 1981; Porter et al. 1983; Evinger 1988). The organization of motoneurons within the oculomotor nucleus is more complex than that described by Warwick (1953; Fig. 6.7a) based on retrograde degeneration experiments. Injections of HRP into the extraocular muscles resulted in the labelling of both sensory and motor neurons supplying individual muscles (Porter et al. 1983). Labelled sensory neurons are restricted to the ophthalmic part of the geniculate ganglion. Each extraocular muscle receives unilateral innervation, with contralateral representation of only the superior rectus and the superior oblique muscles (Fig. 6.7b). The location of medial rectus motoneurons corresponds to the distribution of abducens internuclear terminals (Büttner-Ennever and Akert 1981; Carpenter and Carleton 1983; Fig. 6.7c). The oculomotor nucleus also contains internuclear neurons, which project caudally via the ipsilateral medial longitudinal fasciculus (MLF) and terminate in the contralateral abducens nucleus (Maciewicz et al. 1975; Büttner-Ennever 1977). Horn and co-workers showed that the oculomotor nucleus contains two main categories of motoneurons, innervating twitch muscle fibres, comparable to skeletal muscle fibres, and non-twitch muscle fibres giving a more gradual contraction of muscle fibres, respectively (Horn et al. 2008). The non-twitch motoneurons are situated at the periphery of or outside the main motor nucleus (Fig. 6.7b). In macaque monkeys, levator palpebrae superioris muscle motoneurons are located in the **central caudal nucleus**, a compact unpaired nucleus situated dorsal to the caudal pole of the oculomotor nucleus and the rostral pole of the trochlear nucleus (Warwick 1953; Evinger 1988; Porter et al. 1989; Schmidtke and Büttner-Ennever 1992; van der Werf et al. 1997). This nucleus was first identified in humans by Perlia (1889), who thought that it innervated the medial recti muscles, a view that was held until Warwick's experiments.

Ngwa and co-workers (Ngwa et al. 2014) delineated several motoneuron subgroups supplying individual extraocular muscles in the human oculomotor nucleus using immunostaining for choline acetyltransferase, glu-

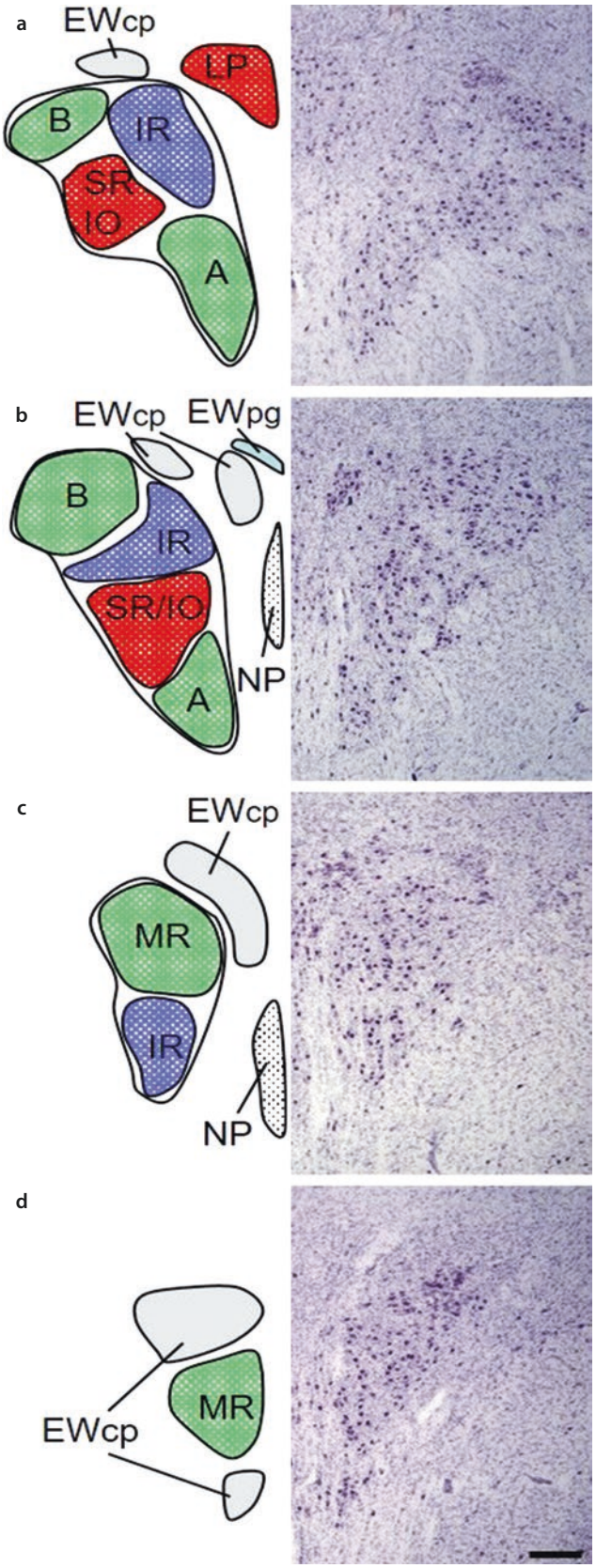


Fig. 6.8 Proposed map of the motoneurons for individual human extraocular muscles at four representative planes from caudal to rostral (**a–d**; from Ngwa et al. 2014 Front Neuroanatomy 8:2, with permission; courtesy Anja Horn, Munich). The right halves show corresponding Nissl-stained sections. EWcp centrally projecting neurons of Edinger-Westphal nucleus, EWpg preganglionic neurons of Edinger-Westphal nucleus, IO inferior oblique motoneurons, IR inferior rectus motoneurons, LP levator palpebrae superioris motoneurons in central caudal nucleus, MR medial rectus motoneurons, NP nucleus of Perlia, SR superior rectus motoneurons

tamate decarboxylase, calretinin and glycine receptor (Fig. 6.8): (1) the central caudal nucleus (CCN); (2) a dorsolateral group (DL); (3) a dorsomedial group (DM); (4) a central group (CEN); (5) a ventral group (VEN); (6) the nucleus of Perlia (NP); and (7) the non-preganglionic centrally projecting Edinger-Westphal nucleus (EWcp). Based on location and immunohistochemistry of the motoneuron subgroups in monkeys, CEN is considered containing the superior rectus and inferior oblique motoneurons, DL and VEN the B- and A-group of medial rectus motoneurons, respectively, and DM the inferior rectus motoneurons. The CCN contains the levator palpebrae superioris motoneurons, whereas the NP may contain upgaze motoneurons.

Lesions affecting the ***oculomotor nerve*** or its rootlets result in ipsilateral oculomotor paralysis (see ▶ Clinical Case 6.2). ***Oculomotor paralysis*** may be isolated (Bogousslavsky et al. 1994; Schwartz et al. 1995) or, more often, occurs in combination with contralateral hemiparesis in which the pyramidal tract in the cerebral peduncle is involved (***Weber syndrome***) or in combination with contralateral ataxia (***Benedikt syndrome*** or upper rubral syndrome and ***Claude syndrome*** or lower rubral syndrome) with involvement of the red nucleus and the superior cerebellar peduncle (see ▶ Clinical Case 6.3). A ***lesion*** of the ***oculomotor nucleus*** leads to a more or less complete oculomotor paralysis of the ipsilateral eye with isolated paralysis of the contralateral superior rectus muscle (Pierrot-Deseilligny et al. 1981b; Pierrot-Deseilligny 2001). The parasympathetic visceromotor branches are located peripherally in the oculomotor nerve. Ischaemic lesions affect primarily the somatomotor fibres located centrally in the nerve, fed by vasa nervorum, whereas compressive lesions affect first the parasympathetic fibres, causing a fixed and dilated pupil.

The **accessory nucleus of the oculomotor nerve** or **Edinger-Westphal nucleus** consists of several parts (Horn et al. 2008; Büttner-Ennever and Horn 2014): (1) the **preganglionic part** (EWpg), a group of parasympathetic neurons, and part of the oculomotor complex; (2)

a **non-preganglionic, centrally projecting part** (EWcp), containing urocortin-positive neurons with central projections to the lateral septum, raphe nuclei and the spinal cord; and (3) an **anterior medial nucleus**. The axons of the EWpg neurons pass to the ciliary ganglion (◘ Fig. 6.6), where they synapse with postganglionic neurons, which innervate the sphincter pupillae and ciliary muscles. The Edinger-Westphal nucleus forms an important component in the light and accommodation reflexes (see ► Chap. 8). Horn et al. (2008) showed that the parasympathetic motoneurons are not restricted to the borders of the traditional Edinger-Westphal nucleus but are much more scattered.

The **trochlear nucleus**, located behind the inferior colliculus (◘ Fig. 6.6e), innervates the contralateral superior oblique muscle. A ***lesion*** in the ***brain stem*** may affect the trochlear nerve nucleus or rootlets (Guy et al. 1989). Damage to the trochlear nucleus and its fibres causes a flaccid paralysis and atrophy of the contralateral (a lesion proximal to the decussation) or ipsilateral (distal to the decussation) superior oblique muscle, resulting in diplopia greatest on downward gaze to the opposite side, with mildly visible external rotation of the eye. The patient tills the head to the contralateral side of the paretic muscle to decrease diplopia and has problems going downstairs and with reading. The nerve can be damaged by an aneurysm of the posterior cerebral or superior cerebellar arteries and during its further course such as in cavernous sinus syndromes and in the superior orbital fissure syndrome (see ► Clinical Cases 6.3 and 6.4).

The **abducens nucleus** lies in the pontomedullary tegmentum of the hindbrain and together with the internal genu of the facial nerve forms a dorsal protrusion into the fourth ventricle, known as the facial colliculus (◘ Fig. 6.6f). The abducens nucleus contains motoneurons innervating the lateral rectus muscle, internuclear neurons and neurons with projections to the cerebellum (Büttner-Ennever and Horn 2004; Leigh and Zee 2006). The third and last component forms part of the cell groups of the **paramedian tract** (**PMT**), which innervate the flocculus, the paraflocculus and the vermis (Büttner-Ennever et al. 1989a; Büttner-Ennever and Horn 1996; Büttner-Ennever and Horn 2014; see ► Chap. 10). Axons of the internuclear abducens neurons ascend in the contralateral MLF and terminate in the medial rectus subnucleus of the oculomotor nerve (see ◘ Fig. 6.7c). Some forms of the Duane syndrome appear to result from a selective absence of the abducens motoneurons, sparing the internuclear neurons (Hotchkiss et al. 1980; Miller et al. 1982; see ► Clinical Case 6.1).

Lesions affecting the ***abducens nerve rootlets*** in the pontomedullary tegmentum lead to complete paralysis of abduction in the ipsilateral eye. In such lesions, often ipsilateral peripheral facial paralysis and contralateral hemiparesis with sparing of the face are associated, due to damage to the adjacent facial nerve fibres and the pyramidal tract, respectively (see ◘ Fig. 6.6f). The abducens nerve can also be damaged by an aneurysm of the internal carotid, basilar or anterior inferior cerebellar arteries, fractures of the skull base, at the petrous tip (Gradenigo syndrome; see ► Clinical Case 6.3), in the cavernous sinus (see ► Clinical Case 6.4) and in the superior orbital fissure syndrome. After a ***lesion*** of the ***abducens nucleus***, paralysis of all ipsilateral eye movements (Meienberg et al. 1981; Pierrot-Deseilligny and Goasguen 1984; Müri et al. 1996a) is usually associated with an ipsilateral peripheral facial paralysis since the internal genu fibres of the facial nerve pass around the abducens nucleus (see ◘ Fig. 6.6f).

At the skull base, the ocular motor nerves are intimately related to the **cavernous sinuses**, which are located on either side of the sella turcica and are connected across the midline by the intercavernous sinuses. The latter encircle the pituitary stalk and are located within the diaphragma sellae. The venous connections are manifold: rostrally the cavernous sinus receives blood from the orbit and the nasal cavity, over the midline both sinuses are connected by the intercavernous sinuses, and laterally the superior petrosal sinus drains into the cavernous sinus. The outflow is usually directed towards the jugular foramen via the inferior petrosal sinus. The cavernous sinus is essential for the venous drainage of the eye. The internal carotid artery and the abducens nerve pass through the cavernous sinus, and several cranial nerves are closely related to its walls (◘ Fig. 6.9): the oculomotor and trochlear nerves as well as the ophthalmic (V1) and maxillary (V2) nerves are situated in the lateral wall. Disorders within or close to the cavernous sinus result in damage to one or more ocular motor nerves and one or more branches of the trigeminal nerve (see ► Clinical Case 6.4).

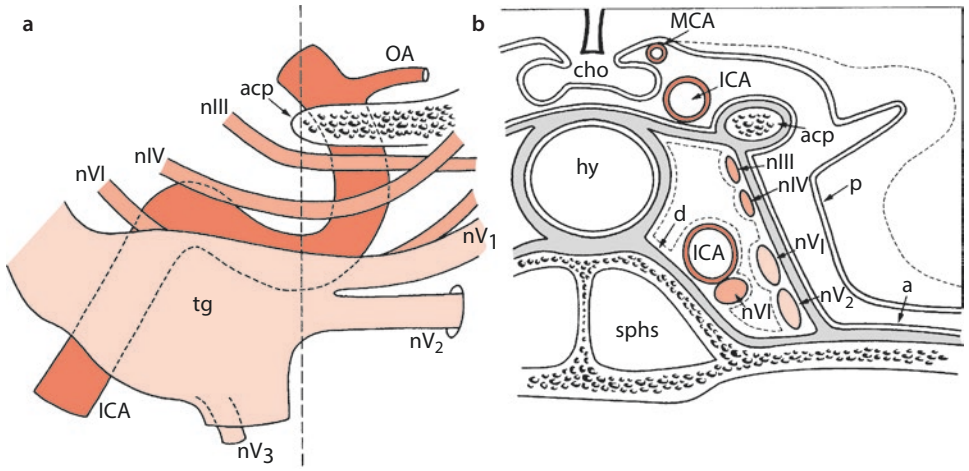


Fig. 6.9 Lateral view **a** and frontal section **b**, showing the intimate relationship of some cranial nerves with the cavernous sinus. The arteries are shown in *red*, the ocular motor nerves in *medium red*, the trigeminal branches in *light red* and the dura mater in *light grey*. a arachnoid, acp anterior clinoid process, cho optic chiasm, d dura mater, hy hypophysis cerebri, ICA internal carotid artery, MCA middle cerebral artery, nIII oculomotor nerve, nIV trochlear nerve, nV1 ophthalmic nerve, nV2 maxillary nerve, nV3 mandibular nerve, nVI abducens nerve, OA ophthalmic artery, p pia mater, sphs sphenoid sinus, tg trigeminal ganglion. (After O'Rahilly 1986, and ten Donkelaar et al. 2007a)

Clinical Case 6.2 Lesions of Individual Ocular Motor Nerves

The ocular motor nerves (the oculomotor, trochlear and abducens nerves) supply the extraocular muscles. ***Acquired ocular motor palsies*** always cause ***diplopia***, except when vision is poor in one eye or suppression in the non-fixing eye has taken place during childhood strabismus. If double vision persists after one eye is covered, the patient has monocular diplopia, which is not a symptom indicating neurological disease. In binocular diplopia, the deviation is maximum with gaze in the direction of the paretic muscle. Ocular symptoms, such as loss of visual acuity, disturbed colour vision (prechiasmatic optic nerve involvement), bitemporal hemianopia and homonymous hemianopia need to be assessed. Neurological findings further increase the probability of establishing a diagnosis. Headache and/or periorbital pain, ataxia and incoordination, hemiplegia and general complaints, such as fever and malaise, which suggest an inflammatory cause, must also be excluded. Trauma should always be inquired about; ocular motor palsies, involving any of the three ocular motor nerves, are often caused by head injury with or without fractures of the skull.

The clinical importance of an ocular motor palsy is determined largely by the presence of accompanying signs and symptoms. Causes for alarm include papilloedema (raised intracranial pressure), a dilated pupil (oculomotor nerve compression by an aneurysm or neoplasm; see ► Clinical Case 6.3), a constricted pupil (sympathetic pathway involvement: Horner syndrome), acquired nystagmus (pontine or cerebellar damage), visual field defects (space-occupying lesions along the optic pathways (see ► Chap. 8) and decreased corneal sensitivity (trigeminal nerve involvement). A mnemonic may help remember the important symptoms and these clinical signs. "DON'T PANIC with ocular motor palsies, but analyze the risk factors carefully!" (Cruysberg 1992):

History

- D = Diplopia
- = Ocular symptoms
- N = Neurological and general symptoms
- T = Trauma

Examination

- P = Papilloedema
- A = Anisocoria (unequal pupils)
- N = Nystagmus
- I = Incomplete visual fields
- C = Corneal hypoaesthesia

The presence of one or more alarm signals (***PANIC signs***) makes a serious cause very likely. The cause of ***multiple affected ocular motor nerves*** is frequently a metastatic or a primary neoplasm. However, if thorough medical examination suggests that a palsy is isolated (e.g. abducens nerve palsy without other neurological findings), the condition is less likely to be the result of serious intracranial disease. The analysis of disturbed ocular motility is best done by ophthalmological examination and should be documented according to the **Hess screen** to assess the course of ***progression*** of the paresis or paralysis as shown in the **Case reports**.

Case report 1: A 35-year-old male underwent successful ocular surgery because of a traumatic corneal perforation of the left eye. In the postoperative follow-up period, the left pupil remained in mydriasis after sutures were removed

and eye drops were stopped. This was attributed to the ocular trauma and the use of atropine eye drops. However, because ***anisocoria*** has to be considered as a PANIC sign in case of an ocular motor palsy, ocular motility was evaluated with orthoptic examination and Hess-screen registration. Hess-screen registration confirmed an unsuspected ***oculomotor nerve paresis*** (Fig. 6.10a), which in combination with the anisocoria makes a serious cause very likely. MRI studies confirmed a brain tumour (a meningioma).

Case report 2: A 6-year-old girl had a ***torticollis*** with the head tilted to the left for several years. Ocular examination showed a ***trochlear nerve paresis*** of the right eye without other ocular or neurological abnormalities. Hess-screen registration confirmed the trochlear nerve paresis

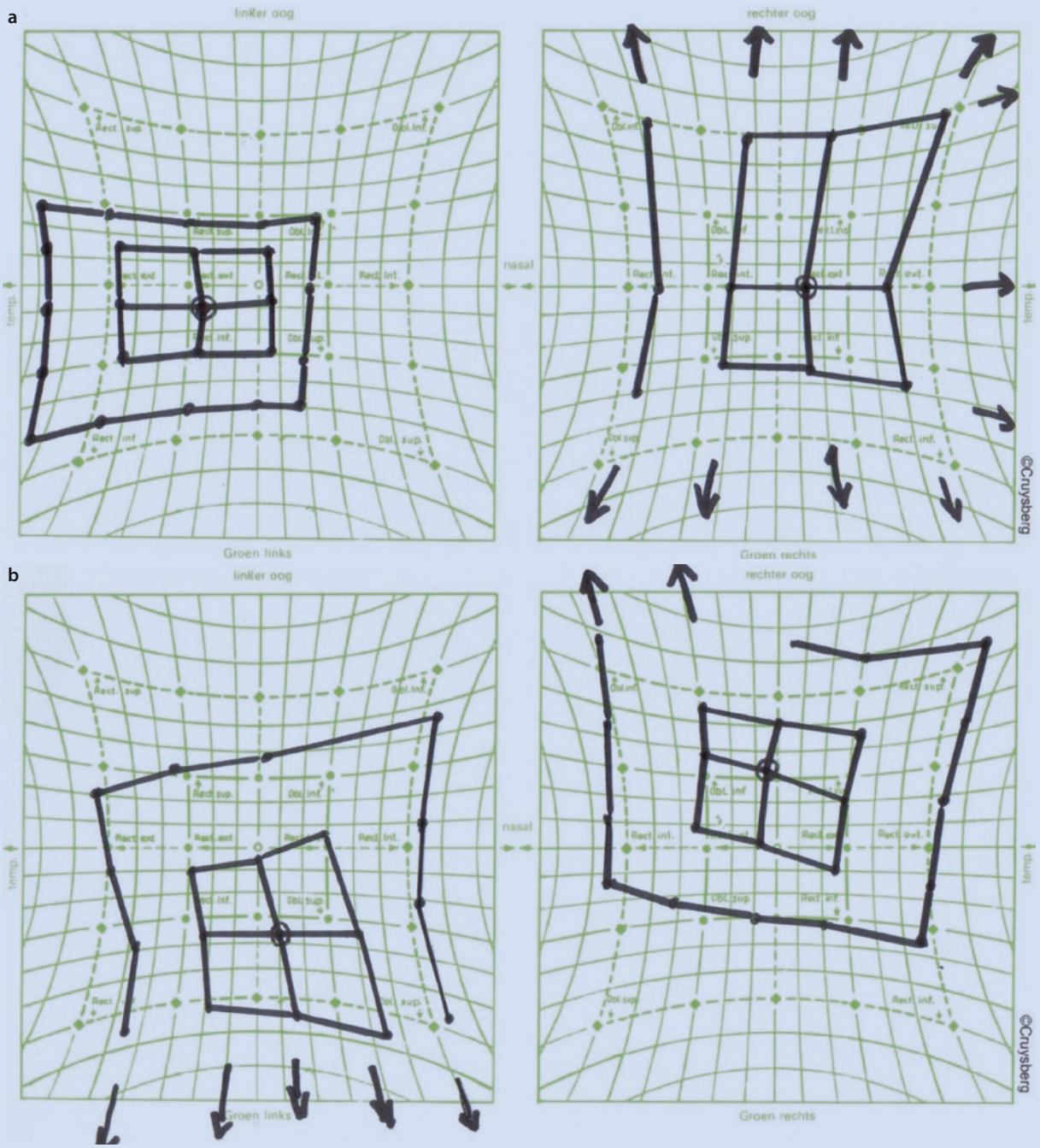


Fig. 6.10 Hess-screen registrations: **a** oculomotor nerve paresis of the left eye; **b** trochlear nerve paresis of the right eye; **c** normal Hess-screen after successful strabismus surgery; **d** abducens nerve paresis. (Courtesy Johannes Cruysberg, Nijmegen)

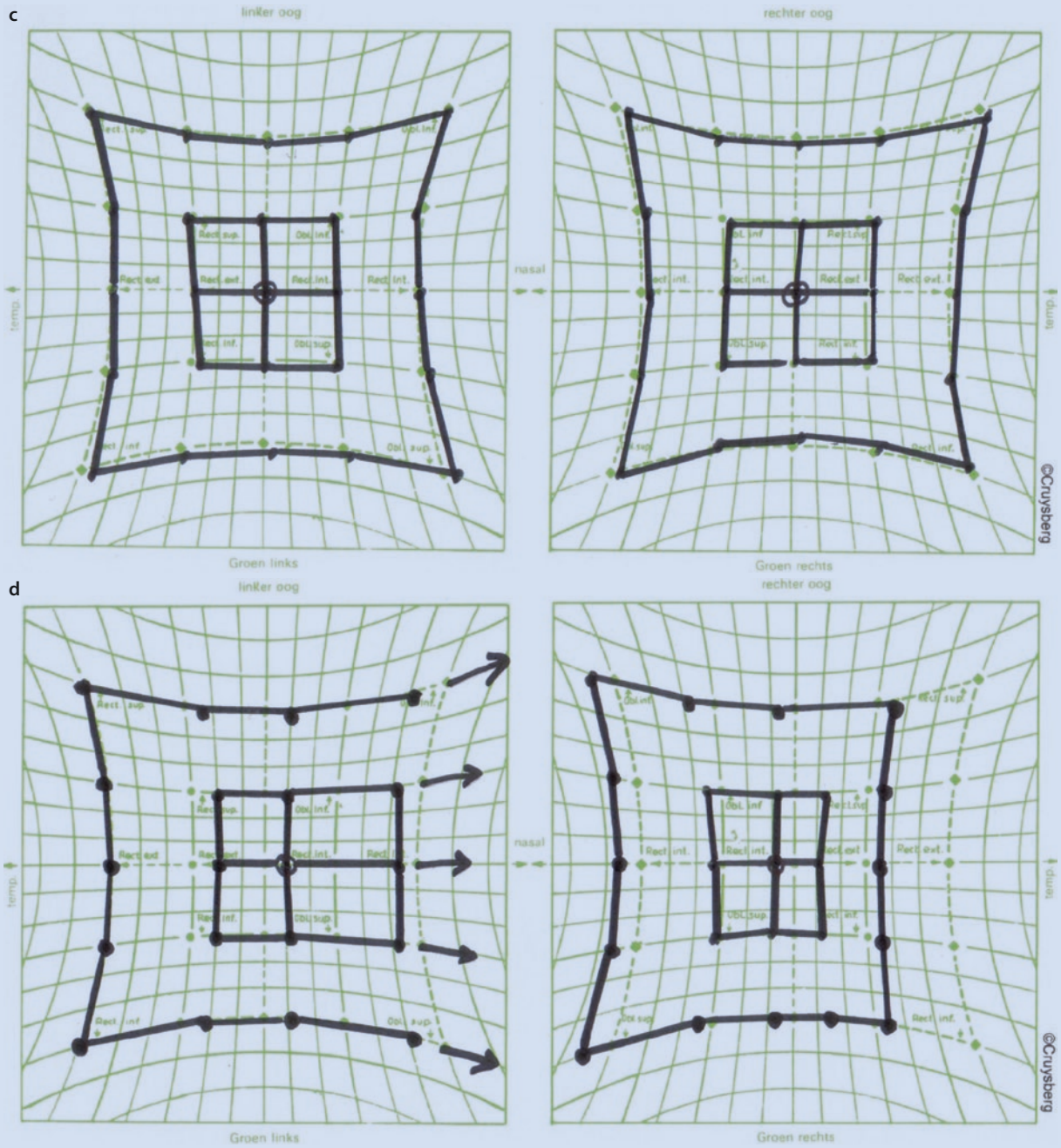


Fig. 6.10 (continued)

of the right eye without any change of ocular motility in a follow-up period of 6 months (Fig. 6.10b). No PANIC signs developed. Strabismus surgery was successful (Fig. 6.10c).

Case report 3: A 44-year-old man visited the Department of Ophthalmology because of ***horizontal diplopia*** in gaze to the right. The patient was diagnosed elsewhere as idiopathic abducens nerve palsy of the right eye, because no abnormal neurological abnormalities were found. Hess-screen registration confirmed the ***abducens nerve paresis*** of the right eye (Fig. 6.10d). Evaluation of PANIC signs disclosed ***corneal hypoaesthesia*** of the right eye, suggesting a serious cause. New imaging studies revealed a right intracavernous aneurysm.

Selected Reference

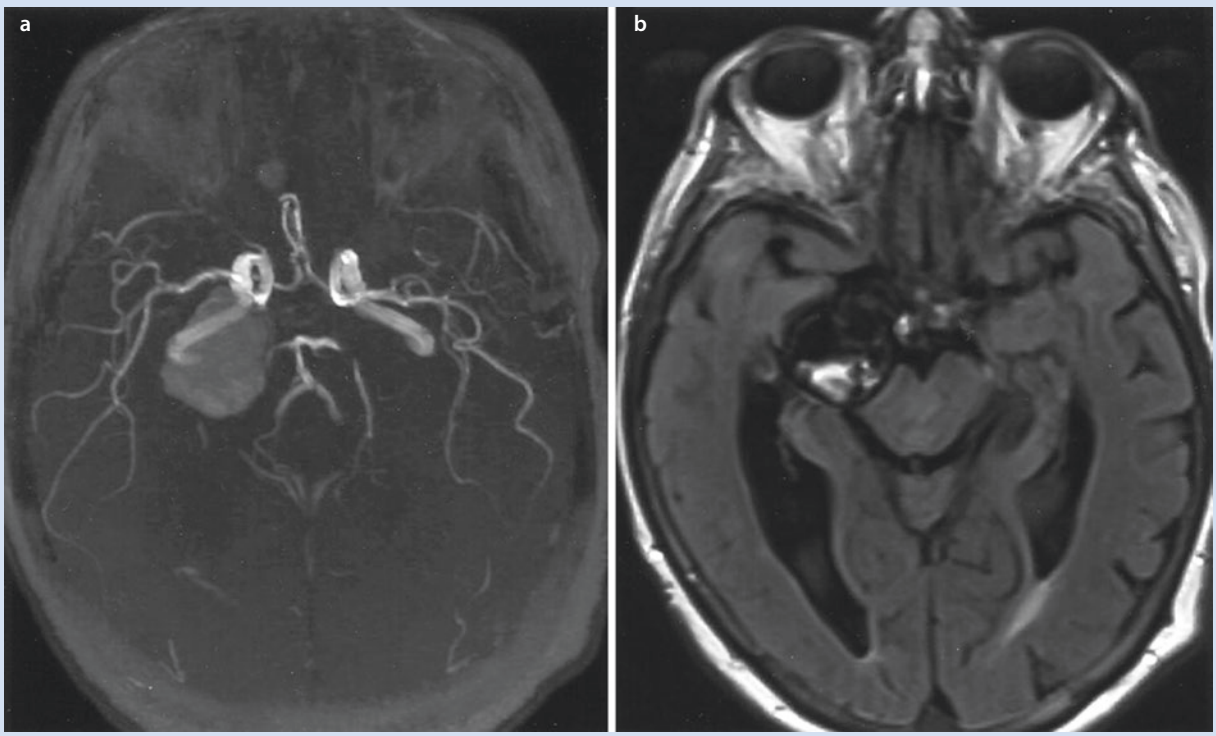
- Cruysberg JRM (1992) DON'T PANIC with ocular motor palsies. Lancet 340:1540

Clinical Case 6.3 Lesions of the Oculomotor Nerve and Nucleus

The IIIth, IVth and VIth cranial nerves control the upper eyelids, the eye movements and the pupils. They run a generally converging course towards the apex of the orbit from widely separate origins in the brain stem (see ◘ Fig. 6.5). Their long intracranial courses make them vulnerable to damage by a wide range of disorders at various sites (Patten 1977; Bone and Hadley 2005):

1. ***Nuclear*** or ***fascicular lesions***, usually with other brain stem damage pointing to the site of the lesion (see **Case report 2**).
2. ***Lesions*** in the ***basilar area*** due to basal meningitis or a basilar aneurysm.
3. ***Lesions*** due to ***aneurysms*** of other arteries such as the posterior communicating artery (see **Case report 1**).
4. ***Lesions*** at the ***petrous tip***, in which only the abducens nerve is vulnerable, due to otitis media or mastoiditis causing diffuse inflammation of the petrous bone and thrombosis of the overlying petrous sinuses; this results in severe ear pain and a combination of lesions of the abducens, facial and vestibulocochlear nerves, known as the ***Gradenigo syndrome***.
5. ***Lesions*** of the cavernous sinus (see ► Clinical Case 6.4).
6. ***Lesions*** at the ***superior orbital fissure*** and the ***orbital apex***, usually due to tumours, meningiomas in particular. Since the three ocular motor nerves are rather close together here, palsies of the IIIrd, IVth and VIth may occur in various combinations. Involvement of the ophthalmic nerve (V1) may cause pain and later numbness in its dermatome with depression of the corneal response (see **Case report 3**).

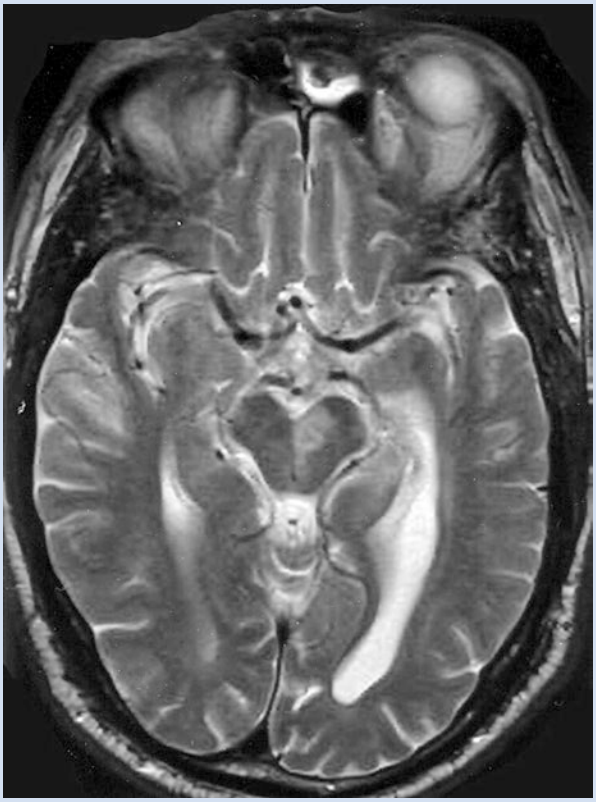
Case report 1: An 88-year-old lady was first seen at the age of 88 for right oculomotor palsy. She was treated for trigeminus neuralgia before by an anaesthesiologist. Her further medical history was inconspicuous. On imaging, a large aneurysm of the right posterior communicating artery was found (◘ Fig. 6.11a, b), which is a well-known cause of oculomotor nerve compression. She did not want to be treated surgically. In the course of the next years, she gradually developed also some weakness of the left side of the body due to compression of the right cerebral peduncle which caused incidental falling. Nonetheless, she remained self-supporting until the age of 88, when she decided to go to a rest-home.



◘ **Fig. 6.11** **a**, **b** MRAs showing a large aneurysm of the right posterior communicating artery compressing the oculomotor nerve. (Courtesy Peter van Domburg, Sittard-Geleen)

Case report 2: A 69-year-old male presented with an invalidating right-sided tremor. He suffered from a hypertensive lacunar stroke 4 months earlier that caused transient right hemiparesis and left oculomotor palsy. Afterwards, he gradually developed a coarse resting tremor of about 3 Hz. The tremor was drug-resistant and gradually evolved into a more particular action and initiation tremor within 1 year. Such a midbrain or Holmes tremor has been attributed to a disruption of the dopaminergic and cerebellar outflow systems (see ▶ Chap. 10). The interval of weeks to years between the initial lesion and the onset is typical. An MRI showed a left-sided paramedian midbrain infarct (◘ Fig. 6.12).

Case report 3: A 79-year-old woman was referred by an ophthalmologist because of progressive loss of vision at the left eye during the last 10 days. She also had double vision but without a consistent pattern and periorbital pain in the previous week. About a year ago she suffered from otitis media but she completely recovered. On examination, there were normal pupillary light reflexes, ptosis at the left side and convergent strabismus in the resting state. Eye-tracking movements at the right were normal and restricted in all directions for her left eye. She had a numb feeling in the dermatome of the ophthalmic nerve, whereas other cranial nerve functions were normal. Hoarseness appeared to be due to hyphal threads on the vocal cords. The contrast-enhanced MRI of the head (◘ Fig. 6.13) showed an invasive retro-orbital mass, spreading from the cavernous sinus into the left orbit, surrounding the optic nerve and the ocular motor nerves in their distal trajectories. This combination of symptoms was diagnosed as ***orbital apex syndrome*** since both the optic nerve and the ocular motor nerves as well as the ophthalmic nerve were involved. A biopsy showed that this process was caused by invasive aspergillosis, apparently rekindled after a latent phase in upper airway structures. She was normally immune competent and responded well to antifungal treatment.



◘ **Fig. 6.12** Flair MRI of a left-sided paramedian midbrain infarct resulting in a left oculomotor palsy. (Courtesy Peter van Domburg, Sittard-Geleen)

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- Bone I, Hadley DM (2005) Syndromes of the orbital fissure, cavernous sinus, cerebellopontine angle, and skull base. J Neurol Neurosurg Psychiatry 76 (Suppl III):iii29-iii38
- Geerlings RPJ, van Domburg PHMF (2014) Orbital apex syndrome caused by aspergillosis. Tijdschr Neurol Neurochir 115:176–181
- Patten J (1977) Neurological Differential Diagnosis. Harold Starke, London, and Springer, London-Berlin

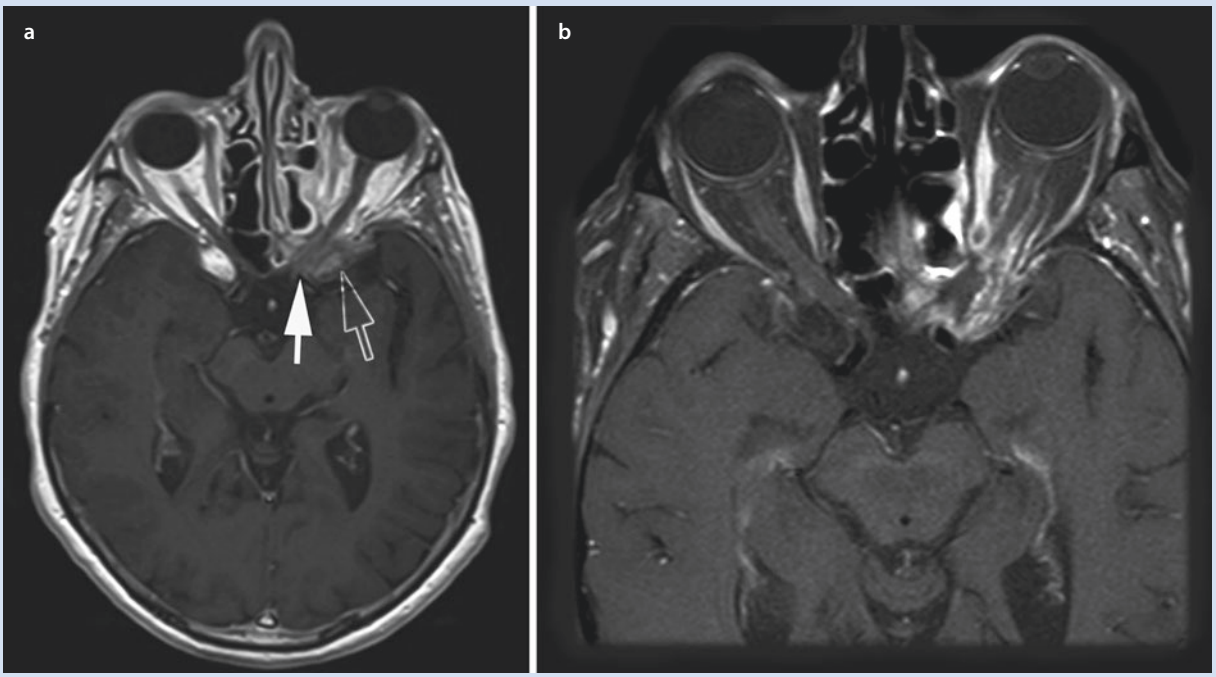


Fig. 6.13 **a** Axial gadolinium contrast enhanced T1-weighted MR images showing an abnormal mass invading the left orbita from the anterior part of the cavernous sinus, guided by the optic nerve (*white arrow*: optic canal) and ocular motor nerves passing through the superior orbital fissure (*open arrow*); **b** fat-suppression sequence with optimal contrast; the contrast enhanced internal carotid artery can be seen as a point of reference. (Courtesy Peter van Domburg, Sittard-Geleen)

Clinical Case 6.4 Cavernous Sinus Syndromes

Various pathological processes may affect the cavernous sinus (Fig. 6.9), collectively known as ***cavernous sinus syndromes***. The relation of the sinus with the deep nasal and orbital venous structures allows the extension of inflammatory processes such as a nasal furuncle ("furunculus mortis") towards the cavernous sinus and may lead to thrombosis. A space-occupying lesion within the cavernous sinus may become manifested by retro-orbital pain in combination with the loss of function of one or more of the four nerves in question. Examples are an aneurysm of the cavernous segment (C4) of the ICA and a metastasis of a malignancy within the sinus. The neurological symptoms and signs should be differentiated from a ***superior orbital fissure syndrome***. In the superior orbital fissure, the four nerves are also in close relation. Here, they may be compressed by a meningioma of the lesser wing of the sphenoid bone. In both instances, the loss of the cornea reflex at the side of the lesion is a characteristic feature. An inflammatory condition of unknown origin affecting the cavernous sinus is the ***Tolosa-Hunt syndrome***.

Case report: A 74-year-old male patient was treated for renal disease, hypertension with left ventricular hypertrophy and a melanoma of the face. He developed complete ophthalmoplegia of the left eye, visual field loss of the left eye, facial paresis and sensory loss of the left face. Further investigations were compatible with left-sided cavernous sinus thrombosis and occlusion of the central retinal vein. MRI showed distention and contrast enhancement of the cavernous sinus and adjacent structures at the left side of the cranial base (Fig. 6.14). There was no recovery on anticoagulation therapy. Laboratory investigation showed hyperhomocysteinaemia. After 1 year, he also developed a left-sided pontine infarct with right hemiparesis for which he had to be admitted to a nursing home, where he died after a few months.

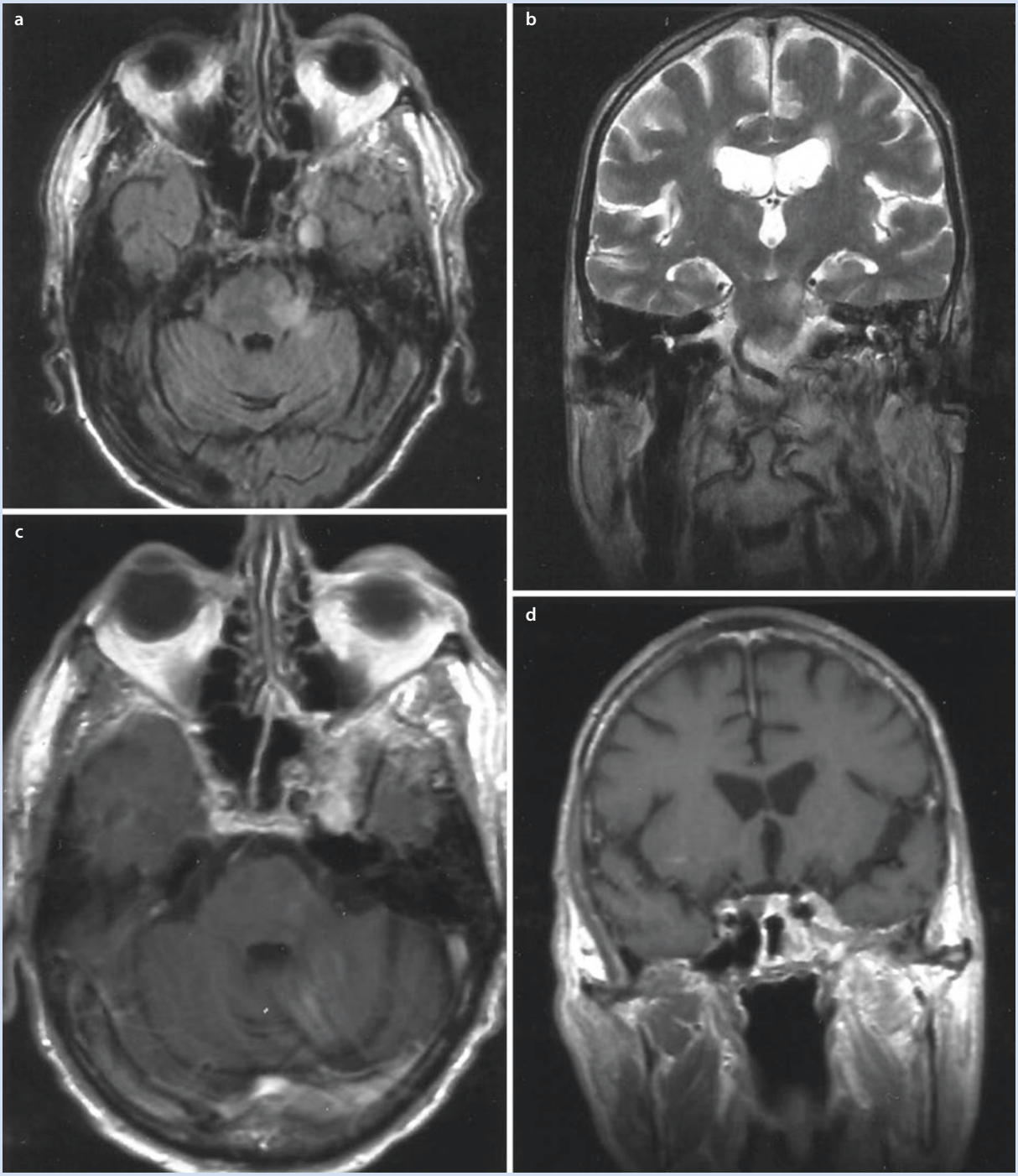


Fig. 6.14 **a**, **c** Axial and **b**, **d** coronal MRIs of a left-sided cavernous sinus thrombosis. (From Geerlings and van Domburg 2014, with permission; courtesy Peter van Domburg, Sittard-Geleen)

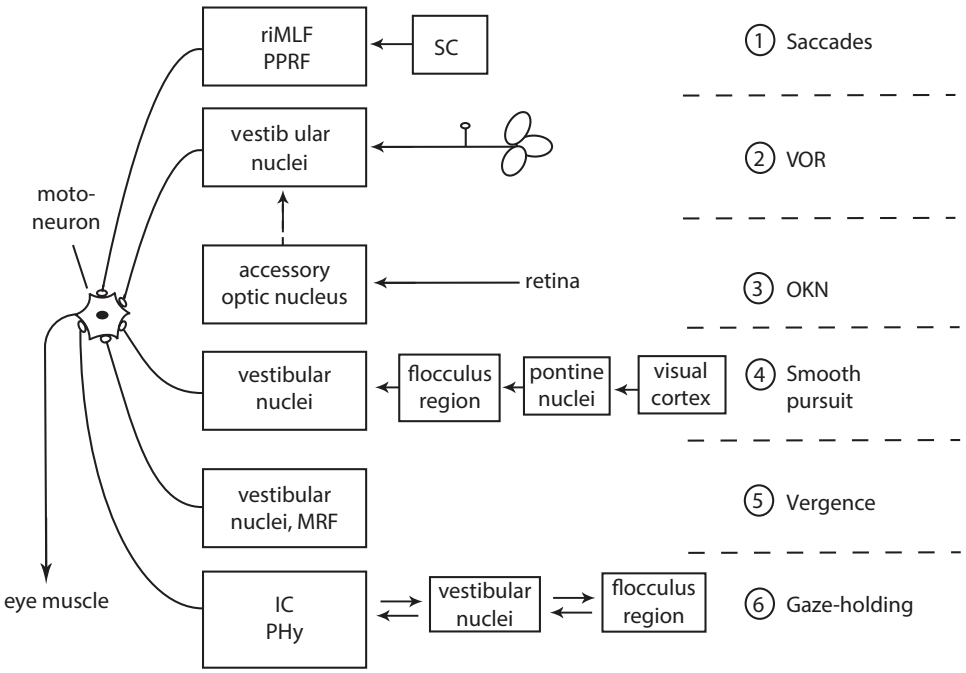
6.4 Eye Movements

Eye movements are highly coordinated and finely tuned; motor units of extraocular muscles include only three to six muscle fibres. Eye movements are in general conjugated and are usually divided into the following types: vestibulo-ocular reflexes, optokinetic responses, saccades, smooth pursuit movements, gaze holding and vergence movements, each of which is thought to be generated by relatively separate oculomotor circuits (Büttner-Ennever and Horn 2004; Leigh and Zee 2006; Horn and Leigh 2011; Horn and Adamczyk 2012). The motoneurons of the oculomotor, trochlear and abducens nuclei form the final common pathway for the control of the extraocular muscles. These nuclei are closely related to particular parts of the reticular formation, to the superior colliculus, the vestibular nuclear complex and the cerebellum. The cerebral cortex and the basal ganglia are involved in visually guided and voluntary eye movements.

6.4.1 Overview

The following functional classes of eye movements are distinguished (Büttner-Ennever and Horn 2004; Leigh and Zee 2006; Horn and Leigh 2011; Horn and Adamczyk 2012; ◘ Fig. 6.15):

1. **Vestibulo-ocular reflexes (VORs)** provide adjustment of the eye position in response to head movements. They are generated by sensory signals from the semicircular canals and the otoliths to the vestibular nuclear complex, which innervates the ocular motor nuclei, mainly via the MLF (see ▶ Sect. 6.4.2). Prolonged stimulation leads to a nystagmus, a rhythmic oscillation of the eyeballs with a slow, compensatory phase alternating with a fast, reset phase. The direction of the nystagmus is named after the fast phase.
2. **Optokinetic responses** hold the image of the seen world steady on the retina during sustained head rotation. They are elicited by the movement of large visual fields across the retina. Extended stimulation in one direction produces optokinetic nystagmus. Such movements across the retina generate responses in the retino-recipient accessory optic terminal nuclei of the mesencephalon (see ▶ Chap. 8). Together with the nucleus of the optic tract in the pretectum, they feed this information into the vestibulo-oculomotor circuits through which the optokinetic responses are generated.
3. **Saccades**, or gaze shifts, are fast, ballistic conjugated eye movements to reset the eye position so that the image of an object in the periphery falls on the fovea. Premotor burst neurons in the paramedian pontine reticular formation activate eye muscle motoneurons during horizontal saccades, whereas those in the rostral interstitial nucleus of the MLF activate the eye muscles during vertical saccades (see ▶ Sect. 6.4.3).
4. **Smooth pursuit movements** are used to follow a moving object so that the image is kept on the fovea. Retinal information reaches via the lateral geniculate body and the primary visual cortex the



◘ **Fig. 6.15** A simplified diagram of the premotor networks subserving five different types of eye movements and gaze holding. All the relatively independent networks converge at the level of the motoneurons of the extraocular eye muscles. IC interstitial nucleus of Cajal, MRF mesencephalic reticular formation, OKN optokinetic nystagmus, PHy perihypoglossal nucleus, PPRF paramedian pontine reticular formation, riMLF rostral interstitial nucleus of the medial longitudinal fasciculus, SC superior colliculus, VOR vestibulo-ocular reflex. (After Büttner-Ennever and Horn 2004)

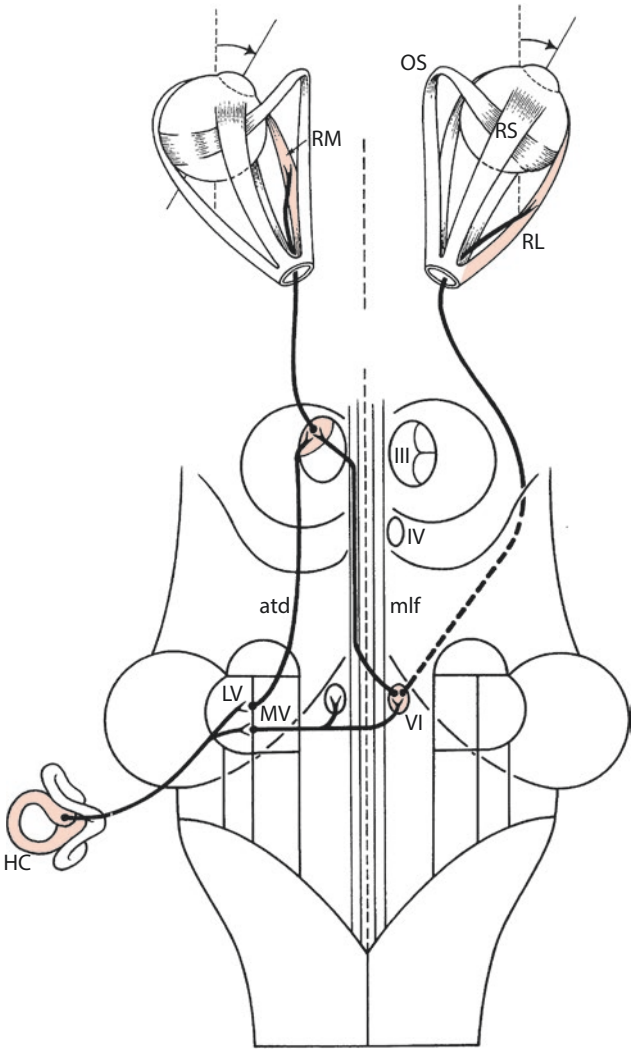
posterior parietal cortex, which via dorsolateral pontine nuclei innervates the dorsal and ventral paraflocculus and the caudal vermis of the cerebellum. Cerebellar efferents generate smooth pursuit movements.

5. **Gaze holding** is used to overcome the elastic properties of the eyeball in the orbit and serves to hold the eye in a new position after a quick movement. Gaze holding circuits include the interstitial nucleus of Cajal and the prepositus hypoglossi nucleus with their reciprocal vestibular and cerebellar connections.
6. **Vergence movements** refer to binocular disjugate movements, during which each eye moves differently to keep the image in the fovea of both eyes when looking at objects at different distances from the viewer. If the object moves towards the viewer, the eyes converge; if the object moves away, the eyes diverge. Vergence premotor neurons have been found in the mesencephalic reticular formation as well as in the pretectum.

6.4.2 The Vestibulo-optokinetic System

The vestibular system stabilizes gaze and ensures clear vision during head movements, especially for those that occur during locomotion. To hold gaze steady, the brain mainly uses labyrinthine and visual cues (optokinetic and smooth pursuit responses), but in patients with vestibular disease, information from muscle spindles and joint receptors may substitute for deficient vestibular signals. Each semicircular duct (see ▶ Sect. 6.8.1) influences a pair of extraocular muscles that move the eyes approximately in the plane of that duct (McCrea et al. 1987a, b; Holstein 2012). A simplified scheme for the horizontal VOR is shown in ◘ Fig. 6.16. Hair cells in the ampulla of the left **horizontal semicircular duct** innervate both excitatory and inhibitory neurons in the medial vestibular nucleus. The projections from the excitatory neurons terminate in the contralateral abducens nucleus, which innervates the right lateral rectus muscle. The left medial rectus muscle is activated via a disynaptic pathway through the left MLF to the oculomotor nucleus. The projections from the inhibitory neurons in the medial vestibular nucleus terminate in the ipsilateral abducens nucleus and inhibit the left lateral rectus muscle and the right medial rectus muscle. Hair cells in the left **anterior** and **posterior semicircular ducts** innervate the superior and medial vestibular nuclei. Their probable connections for the vertical VOR are shown in ◘ Fig. 6.17. Vertical vestibular and pursuit signals ascend to the oculomotor and trochlear nuclei via the MLF.

In normal situations, both labyrinths are stimulated in a reciprocal way that is indicated as a "vestibular harmony". If, however, a disharmonious state of labyrinthine stimulation occurs, either because of loss of function of one labyrinth or because of an overstimulation of the other one, the ensuing stimulation pattern will innervate the oculomotor system in such a way as though a movement of the head is occurring. Actually, a sham movement takes place, but the compensatory vestibulo-ocular reflex will occur all the same. The patient will become aware that he looks away from the object of his attention and will correct the position of his eyes. The continuing misstimulation of the vestibular system will repeatedly induce slow conjugated deviation of the eyes away from the point of fixation and a fast correction movement backwards. This type of eye



◘ **Fig. 6.16** The vestibulo-ocular reflex for horizontal eye movements. The horizontal semicircular canal and the motoneurons and extraocular muscles involved are indicated in *light red*. atd ascending tract of Deiters, HC horizontal semicircular canal, LV lateral vestibular nucleus, mlf medial longitudinal fasciculus, MV medial vestibular nucleus, OS superior oblique muscle, RL, RM, RS lateral, medial and superior rectus muscles, III oculomotor nucleus, IV trochlear nucleus, VI abducens nucleus. (After McCrea et al. 1987a, b)

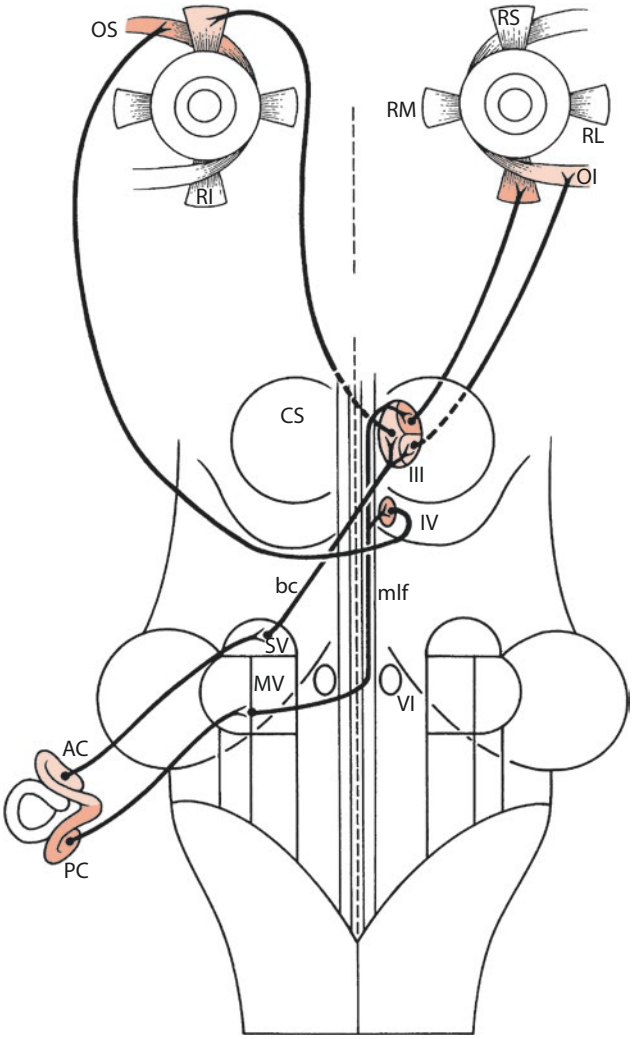


Fig. 6.17 The vestibulo-ocular reflex for vertical eye movements. The anterior semicircular canal and the involved motoneurons and extraocular muscles are indicated in *light red*, the posterior semicircular canal and associated structures in *red*. AC anterior semicircular canal, bc brachium conjunctivum, CS colliculus superior, mlf medial longitudinal fasciculus, MV medial vestibular nucleus, OI, OS inferior and superior oblique muscles, PC posterior semicircular canal, RI, RL, RM inferior, lateral and medial rectus muscles, SV superior vestibular nucleus, III oculomotor nucleus, IV trochlear nucleus, VI abducens nucleus. (After McCrea et al. 1987a, b)

movement disturbance is known as **nystagmus**. Clinically, the nystagmus is named after its fast, corrective component, but actually the slow phase is the pathological one (see ▶ Sect. 6.8.3). The **optokinetic nystagmus** is not related to the vestibular system. It is mediated by the so-called cortical fixation reflex and may be elicited by repetitiously moving objects in a fast sequence past the gaze of the test person. Its presence demonstrates the intactness of the cortical circuits involved (see Konen et al. 2005; Dieterich 2007).

6.4.3 Brain Stem Control of Horizontal and Vertical Eye Movements

The abducens nucleus is the final common pathway for horizontal conjugate eye movements. Its motoneurons innervate the ipsilateral lateral rectus muscle, whereas axons of its interneurons cross the midline to ascend in the MLF to innervate the medial rectus motoneurons of the contralateral oculomotor nucleus (Büttner-Ennever and Akert 1981; Carpenter and Carleton 1983; Horn and Adamczyk 2012). The ocular motoneurons for vertical eye movements lie in the oculomotor and trochlear nuclei. **Premotor burst neurons** in the **paramedian pontine reticular formation** (**PPRF**) activate eye muscle motoneurons during horizontal saccades, whereas those in the **rostral interstitial nucleus of the MLF** (**riMLF**) activate the motoneurons during vertical saccades (Fig. 6.18a). Bilateral chemical lesions of the PPRF selectively abolish horizontal saccades (Henn et al. 1984), whereas bilateral chemical lesions of the riMLF abolish vertical and torsional saccades (Suzuki et al. 1995). Between saccades, the premotor neurons in the PPRF and the riMLF are inhibited by glycinergic **omnipause neurons** (**OPNs**) in the interposed raphe nucleus (Horn et al. 1994) that are tonically active in awake animals (Strassman et al. 1987). Burst neurons and OMNs are innervated by the superior colliculus, whereas the frontal eye fields only contact the omnipause neurons (Moschovakis et al. 1996). In the **PPRF**, two functional subgroups essential for the generation of horizontal saccades have been characterized (Horn et al. 1995; Horn 2006): premotor excitatory burst neurons (EBNs) are glutaminergic and form a compact group of medium-sized neurons in the dorsomedial part of the caudal pontine reticular nucleus, rostral to the level of the abducens nucleus. Inhibitory burst neurons (IBNs) are glycinergic and lie more caudally in the dorsal paragigantocellular nucleus, just caudal to the abducens nucleus (McElligott and Spencer 2000).

In the wing-shaped **riMLF** of monkeys, dorsomedial to the red nucleus, premotor neurons for upward and downward saccades appear to be intermingled (Büttner-Ennever and Büttner 1978; Büttner-Ennever et al. 1982; Moschovakis et al. 1991a, b, 1996; Horn and Büttner-Ennever 1998). Vertical and torsional GABAergic IBNs lie in the region of the interstitial nucleus of Cajal and the riMLF (Horn 2006). All saccadic premotor neurons, labelled transneuronally with tetanus toxin fragment C, and the OPNs contain the calcium-binding protein parvalbumin, which makes it possible to locate the homologue cell groups in the human brain (Horn et al. 1995, 1996, 2000, 2003; see Fig. 6.18b). In macaque monkeys, some neurons medial to the riMLF (the **M-group)** may be related to the coordination of the upper eyelids and eyes

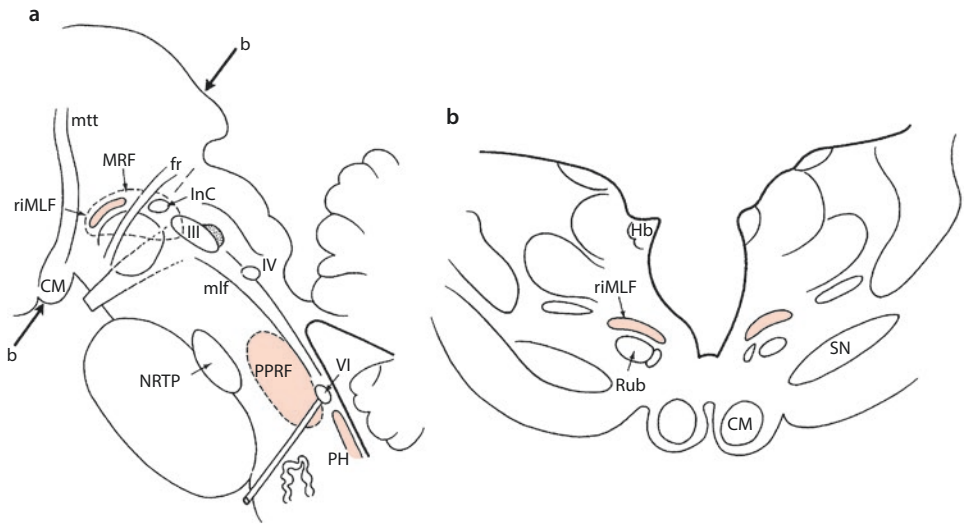


Fig. 6.18 **a** Brain stem centres (in *light red*) involved in the steering of conjugate eye movements (after Büttner-Ennever and Horn 2004) and **b** transverse section through the mesodiencephalon showing the location of the human riMLF. (After Horn and Büttner-Ennever 1998). CM corpus mammillare (mamillary body), fr fasciculus retroflexus, HB habenula, InC interstitial nucleus of Cajal, mlf medial longitudinal fasciculus, MRF mesencephalic reticular formation, NRTP nucleus reticularis tegmenti pontis, PH perihypoglossal nucleus, PPRF paramedian pontine reticular formation, riMLF rostral interstitial nucleus of medial longitudinal fascicle, Rub red nucleus, SN substantia nigra, III oculomotor nucleus, IV trochlear nucleus, VI facial nucleus

during upgaze (Horn et al. 2000; Horn and Adamczyk 2012). In both monkeys and humans, the M-group is strongly parvalbumin-immunoreactive and contains high levels of cytochrome oxidase activity. The **interstitial nucleus of Cajal** (**INC**) is important for vertical gaze holding (Fukushima 1987) and is composed of densely packed parvalbumin-immunoreactive neurons (Horn and Büttner-Ennever 1998). The INC is reciprocally connected with several vestibular nuclei (Carpenter and Cowie 1985b; Kokkoroyannis et al. 1996).

Various ***lesions*** may affect the ***premotor structures***. In monkeys, lesions affecting the ***medial vestibular nucleus*** and the adjacent ***prepositus hypoglossi nucleus*** resulted in severe impairment of fixation and slow eye movements (Cannon and Robinson 1987). Such selective lesions have not been reported in humans. When the medial vestibular nucleus is involved in Wallenberg syndrome, disturbances of the VOR and nystagmus occur (Vuilleumier et al. 1995; Leigh and Zee 2006; Pierrot-Deseilligny 2011). A unilateral ***lesion*** of the ***PPRF*** leads to absence of all ipsilateral saccades, including quick phases of nystagmus, with the result that both eyes remain on the midline. When the lesion affects the caudal part of the PPRF, there also occurs an abducens nerve paralysis, since its rootlets pass through this part of the PPRF.

Lesions of the ***MLF*** between the abducens and oculomotor nuclei result in ***internuclear ophthalmoplegia*** (***INO***). Both horizontal and vertical eye movements are affected, since some of the MLF axons pass from the abducens interneurons to the medial rectus subdivision of the contralateral oculomotor nucleus, whereas other axons carry vestibular and smooth pursuit signals from vestibular neurons to midbrain nuclei for vertical gaze. The lesion may also involve the ipsilateral abducens nucleus, resulting in a "one-and-a-half" syndrome (Pierrot-Deseilligny et al. 1981a), including complete paralysis of lateral conjugate eye movements in one direction (the abducens nucleus lesion) with internuclear ophthalmoplegia in the other direction (the MLF lesion). The eye ipsilateral to the lesion remains immobile during all lateral eye movements, whereas the other eye can only abduct. Many disorders have been reported to cause INO (Leigh and Zee 2006). Unilateral INO is usually related to ischaemia (see also Ewe et al. 2017), whereas bilateral INO is mostly caused by multiple sclerosis (see ► Clinical Case 6.5).

Clinical syndromes with ***vertical eye movement paralysis*** result from lesions affecting the riMLF region. Bilateral lesions, located medially and rostrally to the upper pole of the red nucleus, result in ***downward saccade paralysis*** (***Parinaud syndrome***), with preservation of the downward VOR (Pierrot-Deseilligny et al. 1982). These lesions are usually due to a bilateral infarction in the territory of the posterior thalamosubthalamic paramedian artery (Büttner-Ennever et al. 1989b; see ► Clinical Case 6.6). A unilateral lesion affecting the posterior commissure or the adjacent pretectal region results in ***upward saccade paralysis*** with preservation of the upward VOR (Pierrot-Deseilligny et al. 1982; Ranalli et al. 1988). Large lesions affecting the region of the riMLF bilaterally result in paralysis of upward and downward saccades with preservation of the vertical VOR (Büttner-Ennever et al. 1982; Pierrot-Deseilligny et al. 1982).

Eyelid movements are mediated mainly by the orbicularis oculi and the **levator palpebrae superioris (LPS) muscles**. Dissociated upper eyelid functions exhibit different counterbalanced action of these muscles (Schmidtke and Büttner-Ennever 1992; Büttner-Ennever et al. 1996; Esteban et al. 2004; Skarf 2005; Helmchen and Rambold 2007; Rucker 2011). Three groups of supranuclear motor impairment of eyelid movement may be distinguished:

1. ***Disorders of coordination of eyelid-eye movements***. Nuclei of the posterior commissure control the inhibitory modulation of LPS motoneurons activity and are involved in eyelid-eye coordination disorders such as eyelid retraction observed in Parinaud syndrome (see ► Clinical Case 6.6), parkinsonism and progressive supranuclear palsy (see ► Chap. 11).
2. ***Disturbances of blinking and eyelid "postural" maintenance***. Spontaneous and reflex blinking consists of two components: the inhibition of the basal tonic LPS activity, which keeps the eye open, and the concurrent activation of the orbicularis oculi muscles. Normally, LPS inhibition precedes and outlasts the orbicularis oculi activation. This normal configuration is impaired in parkinsonism and blepharospasm. ***Eyelid postural abnormalities*** include involuntary eyelid closure, usually associated with inability to open the eyes, as found in blepharospasm and blepharocolysis. In ***blepharospasm***, there is involuntary overactivity of the orbicularis oculi muscle with LPS co-contraction activity as expressed as frequent and prolonged blinks, clonic bursts, prolonged tonic contraction or in combination. ***Blepharocolysis***, also known as ***lid-opening apraxia***, is caused by an overinhibition of the LPS with no evidence of ongoing orbicularis oculi activity. Both disorders occur in many instances of idiopathic dystonias and basal ganglia disorders.
3. ***Alteration of voluntary eyelid movements.*** Voluntary eyelid disorders, such as impairment of the Bell phenomenon, voluntary eyelid closure palsy and cerebral ptosis, all related to lesions of the frontal cortical areas.

A lesion anywhere in the brain stem sympathetic chain or the superior cervical ganglion affects the innervation of the superior tarsal muscle of Müller and produces a ***Horner syndrome***, which is characterized by a mild, unilateral ptosis (Skarf 2005).

Clinical Case 6.5 Brain Stem Lesions Affecting Horizontal Eye Movements: INO

The syndrome of a lesion within the MLF, first extensively described in humans by Spiller (1924), consists of paralysis of adduction with preserved convergence of the ipsilateral eye and horizontal nystagmus in the contralateral abducting eye and is known as ***internuclear ophthalmoplegia*** (***INO***). Many disorders have been reported to cause INO (Leigh and Zee 2006). Unilateral INO is usually related to ischaemia, whereas bilateral INO is largely due to demyelination associated with multiple sclerosis (see **Case reports**).

Case report 1: A 29-year-old fireman was seen because of recurrent double vision for 1 week, in particular when looking to the left upper side. It disappeared when he covered one of his eyes. Apart from a left oppressive feeling in his forehead, initially there were no other complaints. Two months later, he also developed slurred speech and loss of control over his left leg. Neurological examination showed a slight convergent skew deviation in the resting state of the eyes. There was paresis of adduction of the right eye, but no evident nystagmus in the left eye when it was abducted. Pupillary diameters and reactions were normal. A possible explanation could be a partial third nerve paralysis of the right eye but also an incomplete INO. On second examination, 2 months later, the ocular signs had disappeared, but a Babinski sign was seen in the left leg. CSF and MRI findings confirmed the diagnosis ***multiple sclerosis***. Apart from brain stem lesions (Fig. 6.19), there were also multifocal signs of demyelination in the semioval centre.

Case report 2: A 57-year-old male was seen at an emergency department after he suddenly experienced severe dizziness with double vision. He had no headache or other neurological complaints, apart from unsteady gait. He suffered from a small stroke some years ago with transient weakness of the right body side. He was treated for hypertension and hypercholesterolaemia and received anti-platelet therapy. Neurological examination showed slight strabismus divergence, whereas on following finger movements adduction of the right eye was impaired and the left eye showed a nystagmoid abduction movement in the same direction, suggesting unilateral internuclear ophthalmoplegia. MRI showed confluent signal disturbances in the brain stem (Fig. 6.20a), whereas diffusion-weighted images showed a diffusion deficit located in the MLF (Fig. 6.20b). At the supratentorial level, some older asymptomatic lacunar ischaemic lesions were present. The patient recovered within a week and he experienced only some dizziness on discharge.

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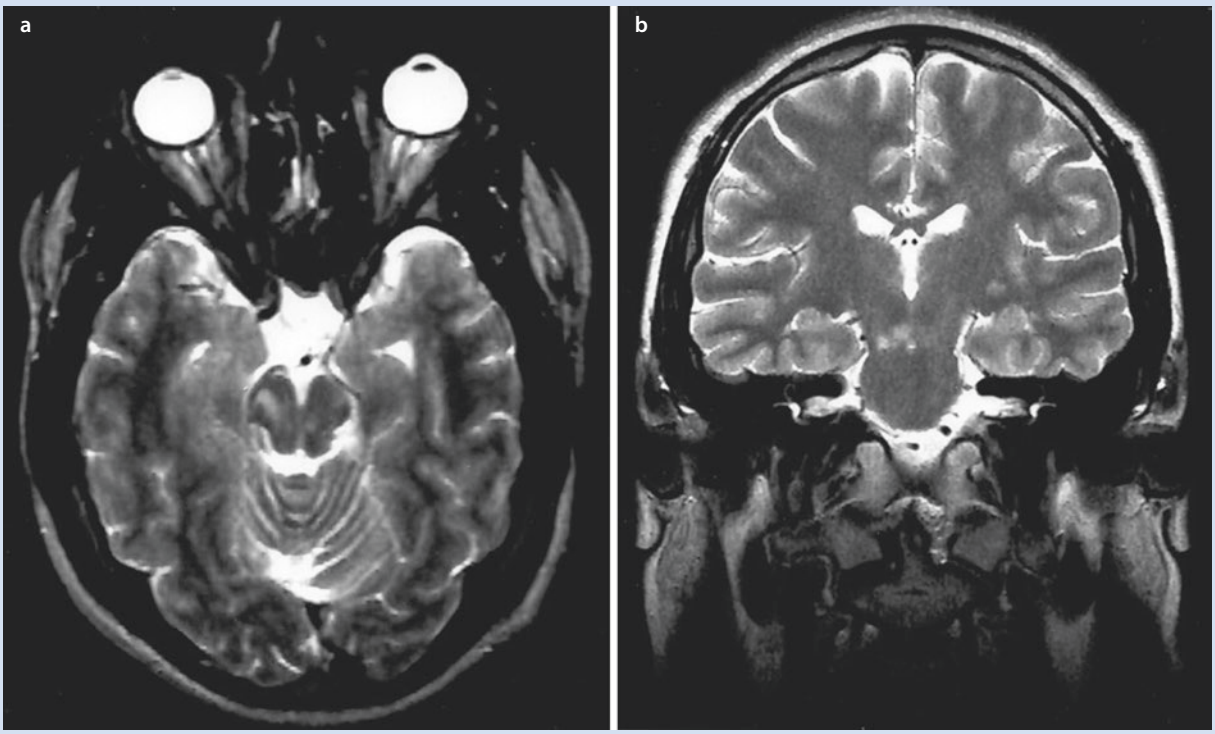

Fig. 6.19 Axial **a** and coronal **b** T2-weighted MRIs of a case of ***internuclear ophthalmoplegia*** due to ***multiple sclerosis***. (Courtesy Peter van Domburg, Sittard-Geleen)

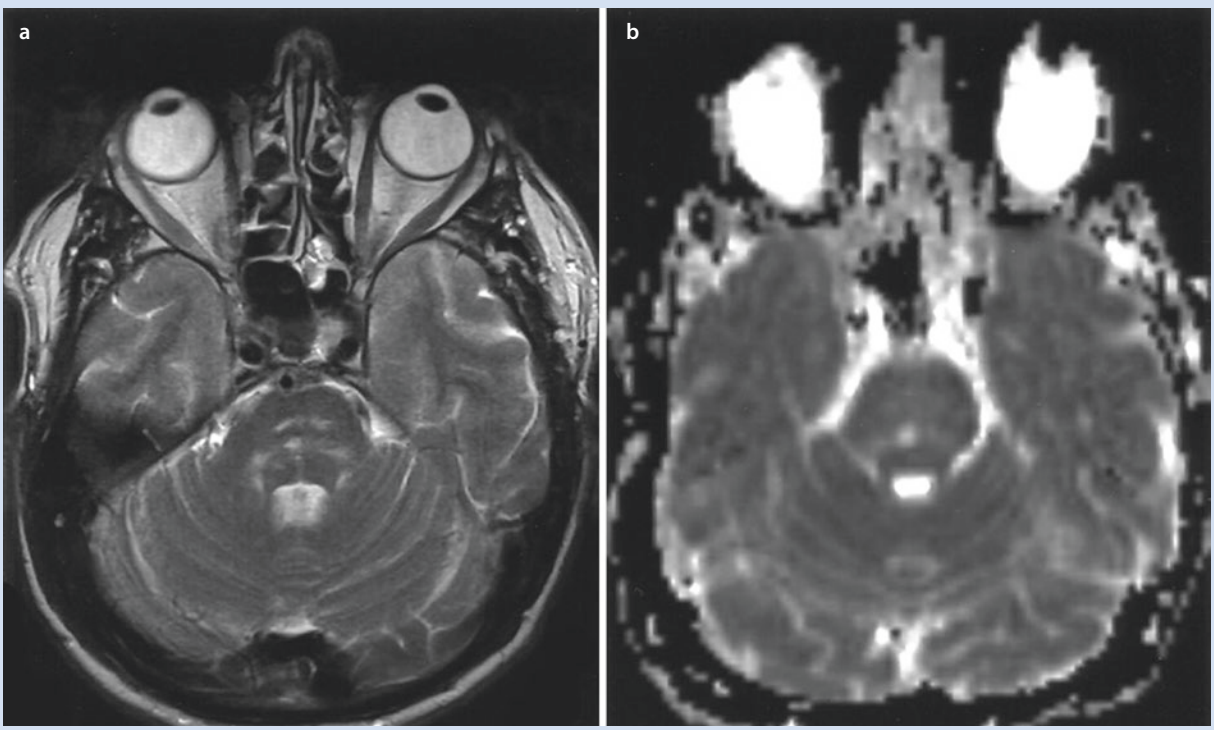

Fig. 6.20 Axial MRI **a** and DWI **b** of a brain stem infarct causing ***internuclear ophthalmoplegia***. (Courtesy Peter van Domburg, Sittard-Geleen)

Clinical Case 6.6 Brain Stem Lesions Affecting Vertical Eye Movements: Parinaud Syndrome

Vertical gaze palsies generally result from tumours or vascular infarcts in the mesodiencephalon. Cases of downward gaze paralysis are rarely seen. Paralysis of upward eye movements alone is relatively common. It is usually combined with disturbances of pupillary light reflexes, accommodation and eyelid retraction, known as ***Parinaud syndrome*** (Parinaud 1883). Büttner-Ennever et al. (1982) discussed six cases with ***isolated paralysis*** of ***downward gaze*** with bilateral lesions from the literature. The region most commonly involved lies around the rostral interstitial nucleus of the MLF (riMLF) and the nucleus of Darkschewitsch. Büttner-Ennever et al. (1982) examined four unilateral lesions giving rise to isolated ***upward gaze paralysis*** from the literature and found that the common lesioned area lies more caudal and ventral than that causing an isolated paralysis of downward gaze. The structures most involved included the posterior commissure and its nucleus, the interstitial nucleus of Cajal and the nucleus of Darkschewitsch. Two unilateral and three bilateral lesions from the literature, giving rise to upward and downward gaze paralysis, were also discussed. For a case of Parinaud syndrome, see the **Case report**.

Case report: A 39-year-old woman experienced acute double vision during a cycle tour. She also had bitemporal headache and could no longer bring her surroundings into focus. Her gait was uncertain, but there were no other focal neurological signs or changes in consciousness or cognition. Her previous medical history was blank, apart from migraine, and she used to smoke a few cigarettes every day. Several first-grade family members had suffered from cardiovascular disease. On admission, she could walk unaided, and there was a divergent strabism of the left eye which only showed some nystagmoid adduction movements. Most prominent were a complete vertical gaze paresis, diminished pupillary reflexes and eyelid retraction. Additional investigations showed hyperglycaemia with elevated HbA1c, which was treated with oral anti-diabetic medication. MR imaging showed a central midbrain lesion (◘ Fig. 6.21). The infarct extended slightly bilaterally into the thalamus, suggesting that it was caused by occlusion of the interpeduncular artery (see ► Chap. 2). Recovery after 1 year was complete.

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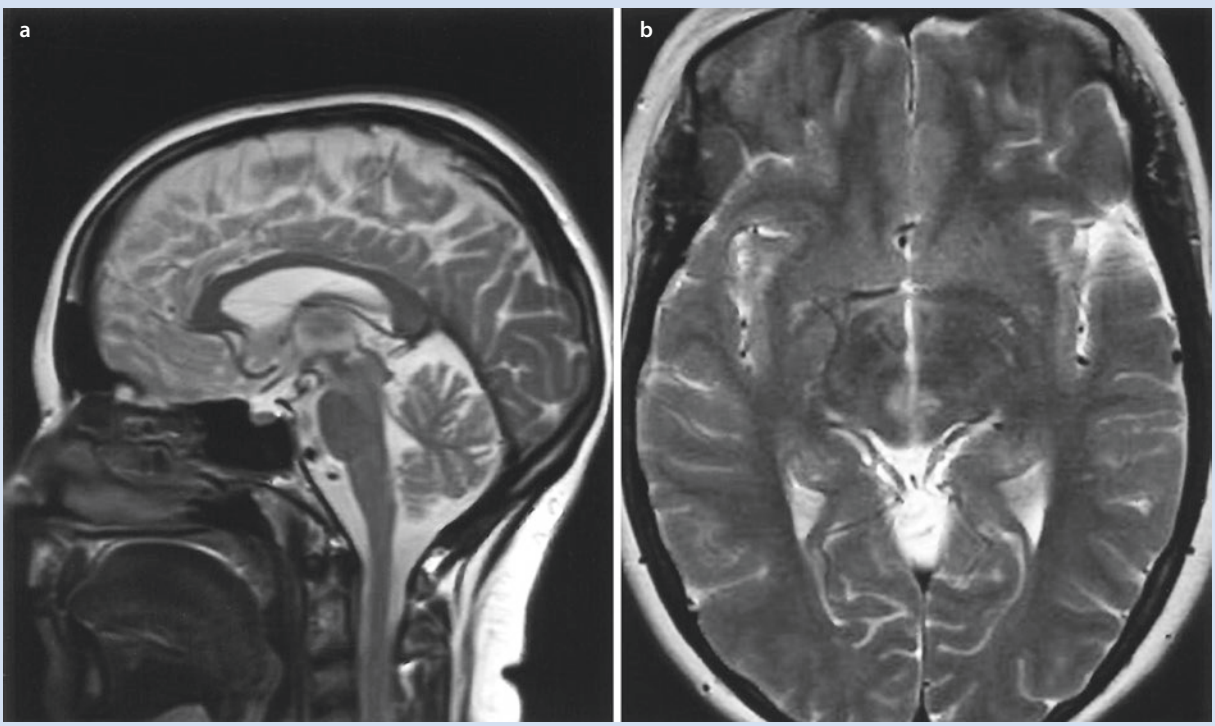
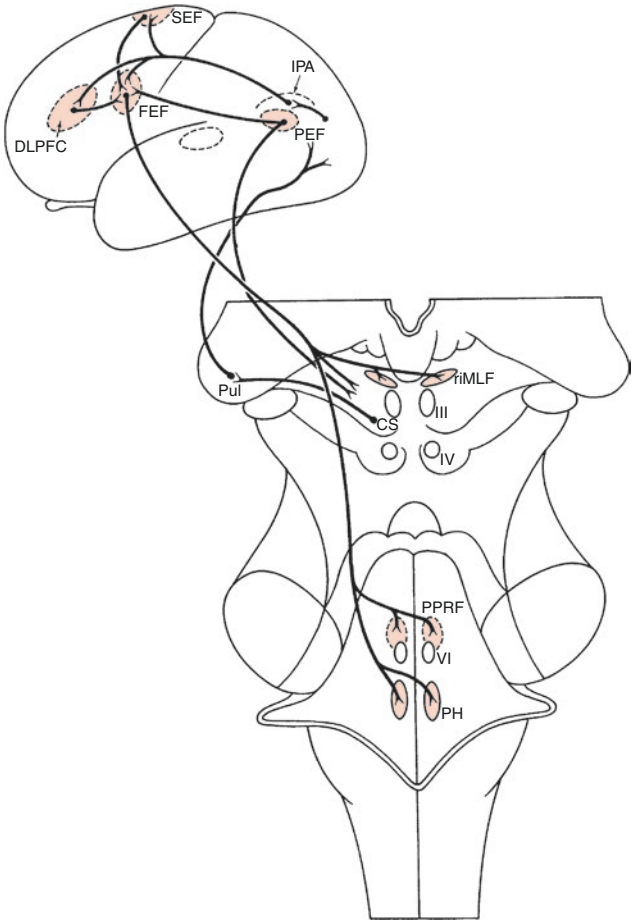


◘ **Fig. 6.21** Sagittal **a** and axial **b** MRIs of a case of ***Parinaud syndrome***. (Courtesy Peter van Domburg, Sittard-Geleen)

6.4.4 Voluntary Control of Eye Movements

Saccades and pursuit eye movements are controlled by different cortical areas. Each hemisphere appears to control eye movements in both lateral directions. Two main cortical areas trigger saccades (Pierrot-Deseilligny et al. 1997): (1) the **frontal eye field** (**FEF**), located in the posterior part of the middle frontal gyrus and the adjacent motor area (Fox et al. 1985), controls intentional saccades, made in the context of learned or remembered behaviour; and (2) the **posterior parietal cortex** (**PPC**), in humans located in the intraparietal sulcus bordering the angular gyrus (Müri et al. 1996b), could be mainly involved in the triggering of reflexive saccades, made to the locations of novel targets suddenly appearing in the external world (Leigh and Zee 2006). The cerebral cortex can trigger saccades via parallel descending pathways to the brain stem reticular formation (Pierrot-Deseilligny et al. 2004; ◘ Fig. 6.22): (1) a direct pathway from the FEF to the premotor burst neurons in the PPRF and riMLF; and (2) a second path from the PPC with a relay in the superior colliculus, before reaching these premotor structures. The frontal lobe contains three areas that contribute to the programming of saccades. FEF neurons discharge before visually guided and memory-related saccades occur. The **supplementary eye field** (**SEF**) in the supplementary motor area seems to be important for the control of sequences of memory-guided saccades and complex oculomotor behaviour. The **dorsolateral prefrontal eye field** (**PFEF**) in the dorsolateral prefrontal cortex may contribute to programming of saccades to remembered target locations. The frontal eye fields project to the superior colliculus, to the brain stem reticular formation and, via pontine nuclei, to the cerebellum. Possibly, also a cingulate eye field in the posterior part of the anterior cingulate gyrus may play a role (see also Coiner et al. 2019).



◘ **Fig. 6.22** Cortical centres involved in the steering of conjugate eye movements (based among others on Pierrot-Deseilligny et al. 2004). CS colliculus superior, DLPFC dorsolateral prefrontal cortex, FEF frontal eye field, IPA intraparietal area, PEF parietal eye field, PH nucleus prepositus hypoglossi, PPRF paramedian pontine reticular formation, Pul pulvinar, riMLF rostral interstitial nucleus of medial longitudinal fasciculus, SEF supplementary eye field, III oculomotor nucleus, IV trochlear nucleus, VI abducens nucleus

In monkeys, saccades can no longer be triggered after bilateral lesions affecting the superior colliculus and the FEF (Schiller et al. 1980). In humans, the same holds for ***lesions*** affecting ***both*** the ***PPC*** and the ***FEF*** (Pierrot-Deseilligny et al. 1988; Dehaene and Lammens 1991; Genc et al. 2004; see ▶ Clinical Case 6.7). ***Posterior parietal lesions*** impair smooth pursuit, predominantly in the ipsilateral direction (Morrow and Sharpe 1990). In monkeys, the **middle temporal visual area** (**MT**) is especially sensitive to visual target motion (see ▶ Chap. 8). Area MT sends this motion signal to the ipsilateral and contralateral **medial superior temporal visual areas** (**MST**). MST cells respond to visual targets moving towards the ipsilateral side (see Leigh and Zee 2006; Horn and Leigh 2011). In humans, these two areas could lie adjacent to each other at the parietotemporo-occipital junction (BA19, BA37 and BA39). A ***unilateral lesion*** limited to ***area MT*** results in contralateral bilateral impairment of smooth pursuit initiation when the target is in the contralateral visual field (Thurston et al. 1988). A ***unilateral lesion*** affecting ***area MST*** results in a decrease in smooth pursuit gain, bilaterally more markedly in the movement directed ipsilaterally to the lesion (Thurston et al. 1988). Lesions affecting the FEF also result in a decrease in ipsilateral smooth pursuit gain (Morrow and Sharpe 1990; Rivaud et al. 1994). ***Bilateral PPC lesions*** result in ***Bálint syndrome***, which includes optic ataxia, peripheral visual inattention and severe deficits of smooth pursuit and reflexive visually guided saccades, whereas intentional saccades persist (Pierrot-Deseilligny et al. 1986; see also ▶ Chap. 15).

Clinical Case 6.7 Paralysis of Saccades and Pursuit

Paralysis of ***saccades*** and ***pursuit*** is characterized by the inability to generate intentional saccades and smooth pursuit in the horizontal and vertical planes. Saccades evoked by vestibular stimulation are present. The syndrome has been described as ***acquired ocular motor apraxia*** (Pierrot-Deseilligny et al. 1988; Genc et al. 2004). The syndrome results from bilateral lesions involving the frontal and the parietal cortex. Dehaene and Lammens (1991) reported one case with postmortem findings (see **Case report**).

Case report: A 73-year-old woman was resuscitated after a cardiac arrest. She rapidly recovered and was examined in the intensive care unit while intubated. Her consciousness was normal. There was no limb paralysis. Facial and eyelid movements were normal, spontaneously as well as on command. The pupillary light reflex was present. There was no hemianopia. Detailed evaluation of neglect was impossible, but neither major visual neglect nor optic ataxia was found. The eyes were in the midline position and immobile. Saccades to command and visually guided saccades were absent in both the horizontal and vertical planes. Sporadically, saccade command elicited a head movement associated with a slow vestibular eye movement in the opposite direction. Smooth pursuit was absent in all directions. Optokinetic stimulation provoked no eye movements. Oculocephalic movements were present. Cold water irrigation of one ear provoked a tonic deviation of both eyes to the irrigated side, with irregular, small corrective saccades in the opposite direction. Convergence was absent. The patient's situation deteriorated after 5 days because of a pulmonary infection. She died 30 days after the appearance of the eye movement disorder. Evaluation of volitional eye movements became impossible because of sedation.

At autopsy, atheromatous plaques were seen in both carotid arteries but without stenosis. There was a severe coronary atheromatosis and a recent myocardial infarction. The brain stem with the collicular area was normal. Circumscribed areas of ***pseudolaminar necrosis*** were found in the superior bank of the left inferior frontal sulcus (the middle frontal gyrus), immediately rostral to the precentral gyrus, and in the upper and lower banks of the left intraparietal sulcus, involving the angular gyrus. The left frontal lesion (Fig. 6.23a) was 7 mm long in the coronal plane and present in only one section, with slices taken every 5 mm. The left parietal lesion (Fig. 6.23b) had a length of 15 mm in the coronal plane and was seen in two consecutive sections. On the right side, several cortical microinfarctions were seen in the depth of the right inferior frontal sulcus, involving both banks, rostral to the precentral gyrus, and in the depth of the intraparietal sulcus, involving the angular gyrus. All the lesions were compatible with a 30-day-old ischaemia and were interpreted as borderzone infarcts after systemic hypotension.

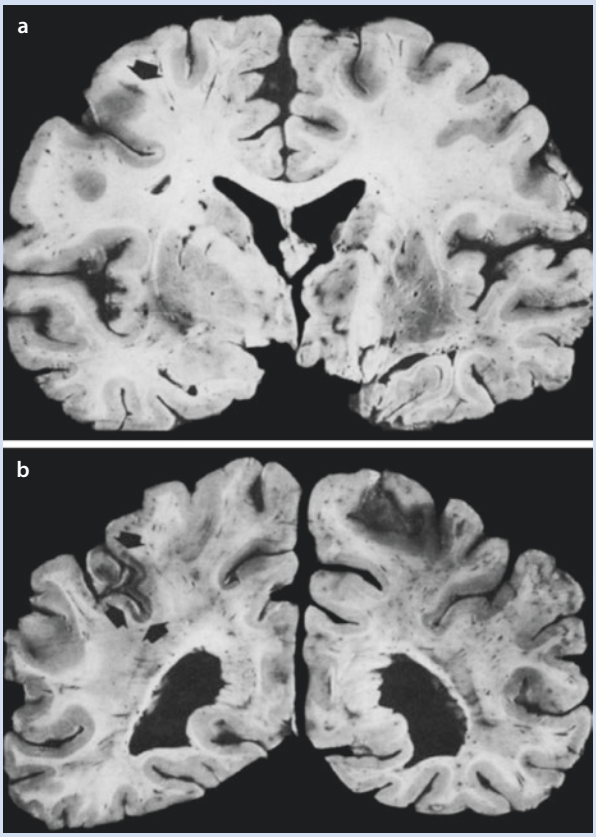


Fig. 6.23 ***Pseudolaminar necrosis*** in the superior bank of the left inferior frontal sulcus **a** and in the upper and lower banks of the left intraparietal sulcus **b** following cardiac arrest. (From Dehaene and Lammens 1991; courtesy Martin Lammens, Edegem)

This case clearly shows that small bilateral cortical lesions in the posterior part of the middle frontal gyri (the frontal eye fields) and in the inferior parietal lobules (the parietal eye fields) can completely abolish intentional saccades and smooth pursuit eye movements.

This case was kindly provided by Martin Lammens (Department of Pathology, University of Antwerpen Hospital, Edegem).

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6.5 The Trigeminal Nerve

6.5.1 The Sensory Portion of the Trigeminal Nerve

The **trigeminal nerve** is a mixed nerve that supplies the skin and mucous membranes of the face and the teeth with sensory fibres (the **sensory root** or **portio major**) and innervates the masticatory muscles via its **motor root** or **portio minor**. The entrance of the trigeminal nerve at the midpontine level can easily be visualized by MRI (Fig. 6.24). The nerve emerges from the brain stem ventralwards into the prepontine cistern and passes under the superior cerebellar artery to enter the trigeminal cavity of Meckel, housing the trigeminal ganglion. The main branches of the nerve are shown in Fig. 6.25a and the respective dermatomes in Fig. 6.25b. Somatosensory fibres in the large trigeminal or semilunar ganglion have peripheral branches in the three main divisions: the ophthalmic, maxillary and mandibular nerves. The central processes of the ganglion cells terminate in the three sensory trigeminal nuclei, spinal, main sensory and mesencephalic (see ► Chap. 4).

The **ophthalmic nerve** (**V1**) gives off a **tentorial** or **recurrent meningeal branch** of Arnold for the tentorium cerebelli and then divides into the lacrimal, frontal and nasociliary nerves, just before the superior orbital fissure (Fig. 6.26a). The **lacrimal nerve** innervates the lacrimal gland, the orbital septum and the conjunctiva and skin of the lateral part of the upper eyelid. The **frontal nerve** gives off two branches: (1) the supraorbital nerve with lateral and medial branches for the mucosa of the frontal sinus and the skin over the forehead and scalp; and (2) the supratrochlear nerve for the conjunctiva and skin of the medial part of the upper eyelid and the skin over the medial part of the forehead. The **nasociliary nerve** gives off the following branches:

1. The **branch to the ciliary ganglion**
2. The **long ciliary nerves** for the ciliary body, the iris and the cornea
3. The small, inconstant posterior ethmoidal nerve
4. The anterior ethmoidal nerve, which gives off (a) internal nasal branches, including the lateral nasal branches for the anterior two-thirds of the lateral nasal wall and medial nasal branches for the mucosa of the anterior third of the nasal septum; (b) an external nasal branch for the skin over the nasal wing and adjacent parts of the nose; and (c) the anterior meningeal branch
5. The infratrochlear nerve for the skin over the lateral part of the nose and the lacrimal sac, the conjunctiva and skin of the medial part of the lower eyelid

The **maxillary nerve** (**V2**) gives off a **meningeal branch** and divides in the pterygopalatine fossa into the

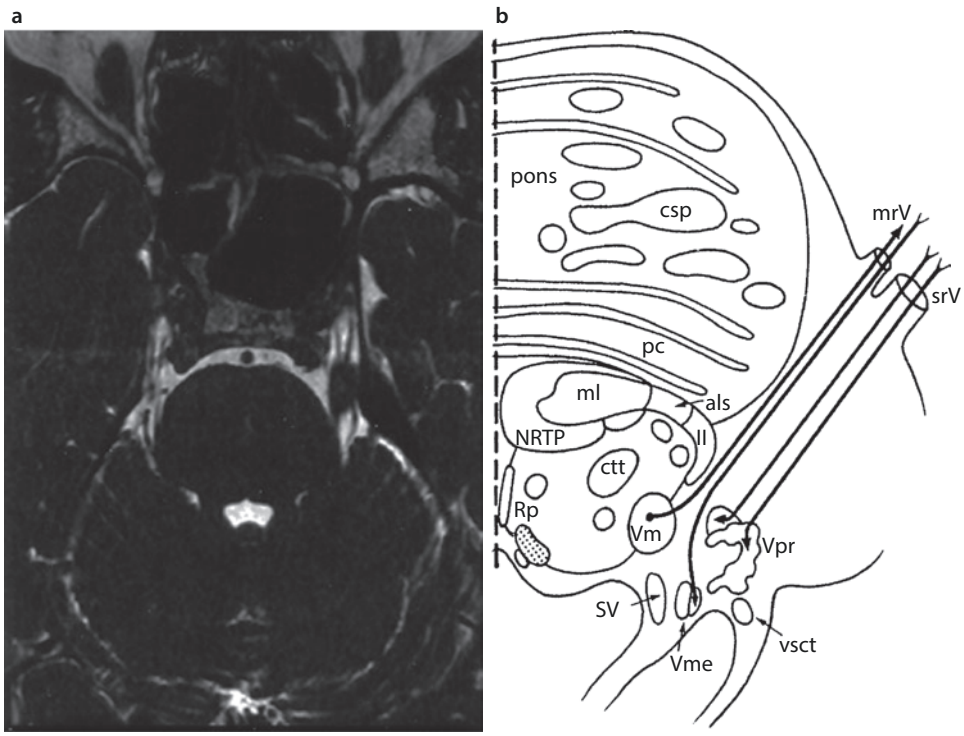

Fig. 6.24 **a** MRI and **b** corresponding horizontal section of the entrance of the trigeminal nerve (**b** based on Duvernoy 1995). The motor root of the trigeminal nerve (*mrV*) arises from the trigeminal motor nucleus (*Vm*) and contains also the fibres of the mesencephalic trigeminal root, located just lateral to the nucleus of that root (*Vme*). The sensory trigeminal root (*srV*) terminates at its level of entrance in the principal sensory trigeminal nucleus (*Vpr*) and passes via the spinal trigeminal tract (medial to Vpr) to the spinal sensory nucleus

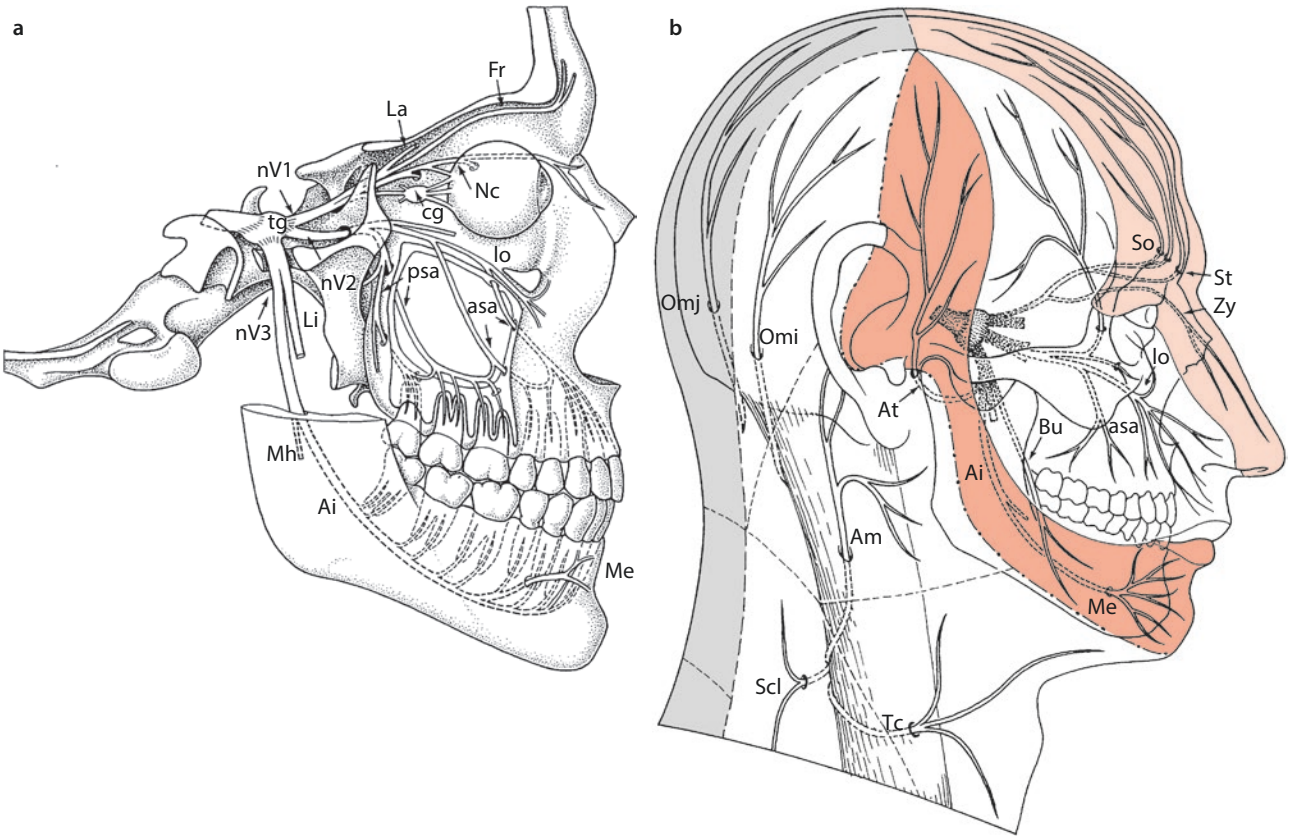

Fig. 6.25 **a** Overview of the trigeminal nerve; and **b** the cutaneous innervation of the head-neck region by the trigeminal nerve (the V1 dermatome is shown in *light red*, the V3 dermatome in *red*), the cervical plexus (C1–C4) and dorsal branches of cervical nerves (in *light grey*). Ai inferior alveolar nerve, Am auricularis magnus (great auricular) nerve, asa anterior superior alveolar branches, At auriculotemporal nerve, Bu buccal nerve, cg ciliary ganglion, Fr frontal nerve, Io infraorbital nerve, La lacrimal nerve, Li lingual nerve, Me mental nerve, Mh mylohyoid nerve, Nc nasociliary nerve, nV1 ophthalmic nerve, nV2 maxillary nerve, nV3 mandibular nerve, Omi lesser (minor) occipital nerve, Omj greater (major) occipital nerve, psa posterior superior alveolar branches, Scl supraclavicular nerves, So supraorbital nerve, St supratrochlear nerve, Tc transversus colli nerve, tg trigeminal ganglion, Zy zygomatic nerve. (After ten Donkelaar et al. 2007b)

infraorbital and zygomatic nerves, posterior superior alveolar branches and **branches to the pterygopalatine ganglion** (Fig. 6.26b). The branches given off by the pterygopalatine ganglion include the greater and lesser palatine nerves, the nasopalatine nerve, nasal branches and the pharyngeal nerve. The **infraorbital nerve** is regarded as the continuation of the maxillary nerve and gives off the following branches: (a) inferior palpebral branches; (b) external nasal branches; (c) internal nasal branches; and (d) superior labial branches for the upper lip. The **zygomatic nerve** gives off (a) the zygomaticotemporal branch for the skin of the temple and (b) the zygomaticofacial branch for the skin over the prominent lateral surface of the zygomatic bone. The superior alveolar nerves comprise (a) the posterior superior alveolar branches; (b) the middle superior alveolar branch; and (c) the anterior superior alveolar branches. Together they form the superior dental plexus, giving off superior dental branches and superior gingival branches.

The **mandibular nerve** (**V3**) gives off a **meningeal branch** and **branches to** the **otic ganglion**. In the infratemporal fossa, it divides into anterior and posterior divisions (Fig. 6.26c). The **anterior division** is largely motor and gives off the following branches:

1. The nerve to the tensor veli palatini muscle
2. The nerve to the tensor tympani muscle
3. A large number of branches to the muscles of mastication: (a) the nerve to the medial pterygoid muscle; (b) the masseteric nerve to the masseter muscle; (c) the deep temporal nerves to the temporalis muscle; and (d) the nerve to the lateral pterygoid muscle
4. The buccal nerve for the innervation of the skin and mucosa of the cheek.

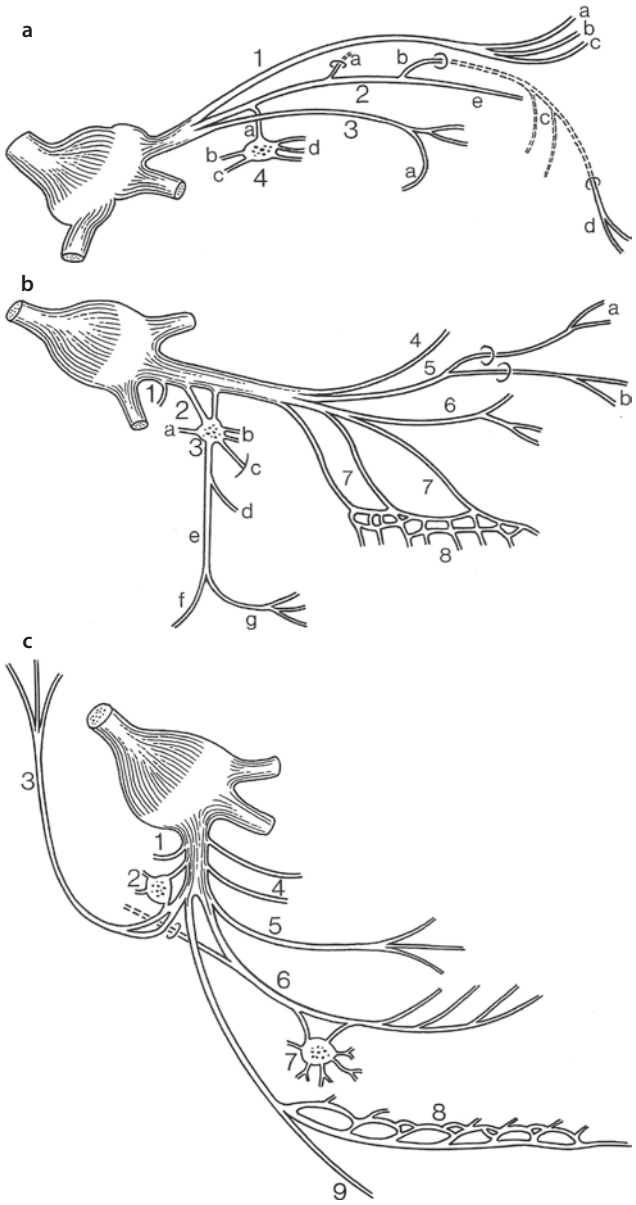

Fig. 6.26 **a** The ophthalmic nerve. *1* frontal nerve with *a* supratrochlear nerve, *b*, *c* medial and lateral branches of supraorbital nerve, *2* nasociliary nerve with *a* posterior ethmoidal nerve, *b* anterior ethmoidal nerve, *c* internal nasal branches, *d* external nasal branch, *e* infratrochlear nerve, *3* lacrimal nerve with *a* communicating branch to zygomatic nerve, 4 ciliary ganglion with *a* communicating branch to ciliary ganglion, *b* sympathetic branch to ciliary ganglion, *c* parasympathetic, oculomotor branch to ciliary ganglion, *d* short ciliary nerves. **b** The maxillary nerve and its branches. *1* meningeal branch, *2* pterygopalatine nerves, *3* pterygopalatine ganglion with the following branches: *a* nerve of pterygoid canal, *b* orbital branches, *c*, *d* superior and inferior posterior nasal branches, *e* palatine nerves, *f* greater palatine nerve, *g* lesser palatine nerves, *4* communicating branch to lacrimal nerve, *5* zygomatic nerve with *a* zygomaticotemporal branch and *b* zygomaticofacial branch, *6* infraorbital nerve, *7* superior alveolar nerves, *8* superior dental plexus. **c** The mandibular nerve and its branches. *1* meningeal branch, *2* otic ganglion, *3* auriculotemporal nerve, *4* branches to masticatory muscles, *5* buccal nerve, *6* lingual nerve receiving the chorda tympani, *7* submandibular ganglion, *8* inferior dental plexus, *9* mylohyoid nerve. (After Hafferl 1957; from ten Donkelaar et al. 2018)

The **posterior division** is largely sensory and gives off the following branches:

1. The **auriculotemporal nerve** with the following branches: (a) the nerve to the external acoustic meatus; (b) branches to the tympanic membrane supplying its external surface; (c) visceromotor parotid branches to the parotid gland; (d) anterior auricular nerves for the tragus and the anterior surface of the auricle; and (e) the superficial temporal branches supplying the skin in the temporal region
2. The **lingual nerve** with the following branches: (a) branches to the isthmus of the fauces; (b) the sublingual nerve for the floor of the oral cavity and the inferior surface of the tongue; (c) the lingual branches for the mucosa of the dorsum of the tongue; (d) the posterior branch to the submandibular ganglion; and (e) comparable inconstant branches to the variant sublingual ganglion
3. The **inferior alveolar nerve** with the following branches: (a) the nerve to the mylohyoid muscle supplying the mylohyoid muscle and the anterior belly of the digastric muscle; (b) the inferior dental plexus with inferior dental branches and inferior gingival branches for the gingiva; and (c) the mental nerve, the terminal branch of the inferior alveolar nerve, with inferior labial branches for the lower lip and inferior gingival branches for the gingiva. Its mental branches supply the skin of the chin.

The most frequent disorder of the trigeminal nerve is ***trigeminal neuralgia***. It starts in the second and third divisions of the trigeminal nerve and affects the cheek or the chin (Bowsher 1997; Love and Coakham 2001). The essential features of idiopathic trigeminal neuralgia are defined by the International Association for the Study of Pain (IASP) as sudden, transient bouts of superficially located pain, strictly confined to one or more divisions of the trigeminal nerve, usually precipitated by light mechanical activation of a trigger point or area. It undergoes spontaneous remissions and recurrences. The majority of cases are caused by vascular compression of the trigeminal nerve at its point of entry into the brain stem (Jannetta 1980; see ▶ Clinical Cases 4.13 and ▶ 6.8). The trigeminal nerve and its branches can also be damaged during their course to the periphery such as in the Gradenigo, petrous tip and superior orbital fissure syndromes (see ▶ Clinical Cases 6.3 and 6.4). ***Ophthalmic herpes zoster***, a viral infection caused by activation of the virus in the trigeminal ganglion, may spread via V1 and cause vesicular eruptions on the skin of the forehead, nose and eyelids but especially on the cornea, resulting in inflammation of the cornea and conjunctiva and ***photophobia***.

Clinical Case 6.8 Trigeminal Neuralgia

Trigeminal neuralgia is a disabling paroxysmal disorder consisting of sudden lightning stabs of pain of short duration, most often localized in the distribution area of the maxillary or mandibular branches of the trigeminal nerve. The majority of cases are caused by vascular compression of the trigeminal nerve at its point of entry into the pons (Jannetta 1977; Love and Coakham 2001; see **Case report**).

Case report: A 75-year-old female presented with neuralgic pain, more in particular of the ophthalmic branch of the trigeminal nerve, but to a lesser degree of the maxillary and mandibular branches. The pain had an episodic course with tingling, itching and sometimes sharp sensations. An MRI in the CISS sequence, accentuating contours instead of parenchymatous details, showed crossing of the elongated superior cerebellar artery with the trigeminal root, as is often seen in the elderly (Fig. 6.27).

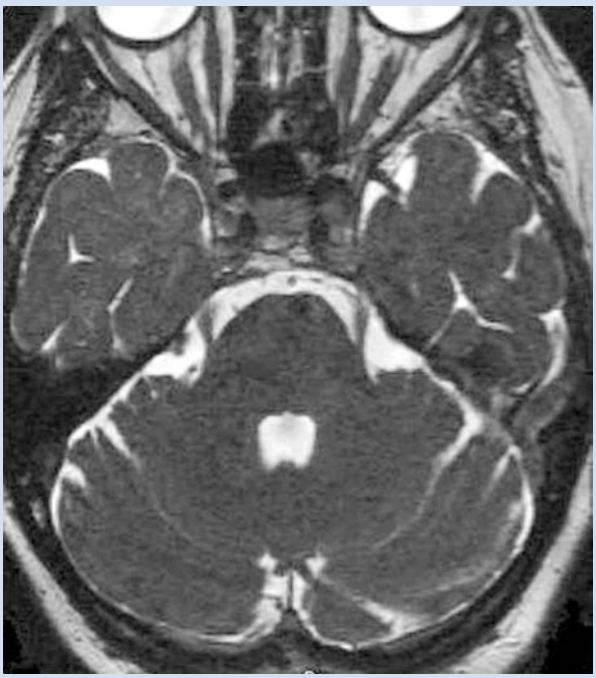

Fig. 6.27 A case of ***trigeminal neuralgia*** due to compression of the trigeminal root by an elongated superior cerebellar artery. (Courtesy Peter van Domburg, Sittard-Geleen)

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6.5.2 The Motor Portion of the Trigeminal Nerve

The masticatory muscles are innervated by the **trigeminal motor nucleus**. The trigeminal, facial and ambiguus motor nuclei form the branchiomotor nuclei. The trigeminal motor nucleus is innervated by various brain stem structures and by the cerebral cortex. In cats, **corticobulbar fibres** terminate predominantly in the lateral tegmental field (Kuypers 1958a), in monkeys and humans also directly in the trigeminal motor nucleus (Kuypers 1958b, c). In cats, Holstege and Kuypers (1977) studied the local bulbar connections to the Vth, VIIth and XIIth motor nuclei with anterograde degeneration techniques. Their findings suggested the presence of a **lateral** and a **medial propriobulbar fibre system** within the lateral tegmental field. The lateral propriobulbar system projects mainly ipsilaterally to these motor nuclei, the medial system bilaterally. With anterograde tracing, the origin of these systems was further substantiated (Holstege et al. 1977). Neurons in the lateral part of the lateral tegmental field form the lateral propriobulbar system and distribute fibres mainly to the ipsilateral bulbar motor nuclei (Fig. 6.28). Neurons in the medial part of the lateral tegmental field form the medial propriobulbar system, which is organized bilaterally and tends to distribute fibres to the motor nuclei bilaterally. The various neuronal cell groups, which project through the medial propriobulbar system to the different motor nuclei bilaterally, show relatively less spatial segregation than those, which project through the lateral system to these motor nuclei. In rats, Fay and Norgren (1997a) studied the **premotor system** of masticatory motoneurons with the transneuronal tracer pseudorabies virus. They confirmed Holstege's data on the propriobulbar systems for the innervation of trigeminal motoneurons in cats, but moreover found a number of other brain stem centres innervating the trigeminal motoneurons. Transneuronally labelled neurons were found in regions already known to project to the trigeminal motor nucleus such as the subcoeruleus nucleus, trigeminal sensory areas, the parvocellular reticular formation and dorsal medullary tegmental fields, but also in many other areas of the brain stem including the periaqueductal grey, the dorsal raphe, the laterodorsal and pedunculopontine tegmental nuclei, the substantia nigra and various parts of the pontine and medullary reticular formation. They

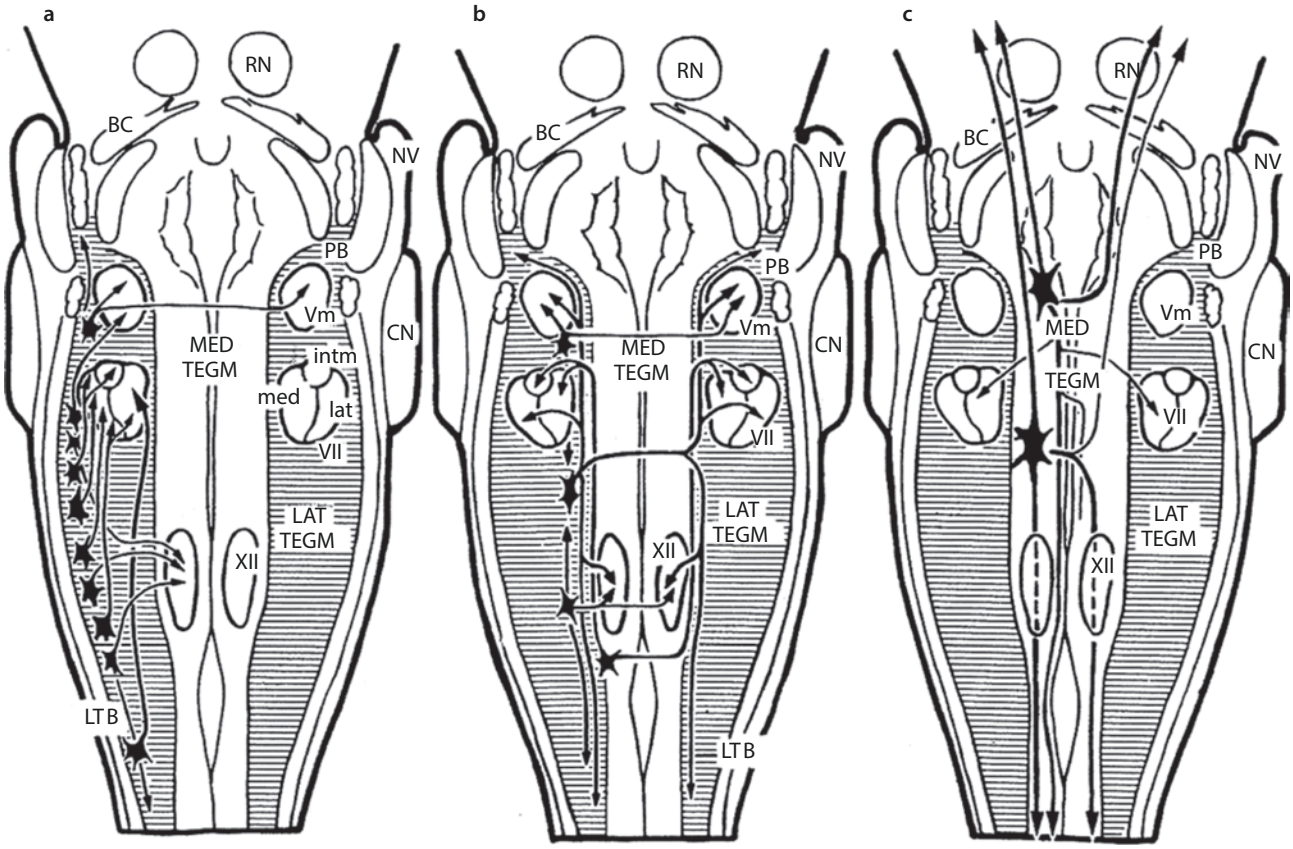

Fig. 6.28 Diagrams showing the distribution of fibres from neurons in the lateral and the medial parts of the bulbar lateral tegmental field to the trigeminal (*Vm*), facial (*VII*) and hypoglossal (*XII*) motor nuclei. Note the mainly unilateral distribution of the fibres from neurons in the lateral part of the motor nuclei (**a**) and the bilateral distribution from neurons in the medial part (**b**). In (**c**), the ascending and descending projections from the medial tegmental field are shown. BC brachium conjunctivum, CN cochlear nerve, LTB lateral tegmental bundle, NV trigeminal nerve, PB parabrachial nucleus, RN red nucleus. (After Holstege et al. 1977)

showed that orofacial muscles (masticatory, facial and lingual) are innervated by a complex, but remarkably uniform network of multisynaptic connections in the brain stem.

In clinical neurophysiology, the following **brain stem reflexes** related to the trigeminal nerve are currently tested: the early (R1) and late (R2) blink reflexes, early (SP1) and late (SP2) masseter inhibitory reflexes, and the jaw reflex (Cruccu et al. 2005). Multiple reflex abnormalities reflect damage of the primary afferent neurons. Cruccu and co-workers studied these brain stem reflexes in 180 patients with focal brain stem infarction. Patients with abnormalities in R1, SP1 and R2 had lesions involving the primary sensory neurons in the ventral pons, before the afferent fibres directed to the respective reflex circuits diverge. Patients with an isolated abnormality of R1 and SP1 responses had lesions that involved the ipsilateral dorsal pons, near the floor of the fourth ventricle. The area with the highest probability of lesion for the R2-afferent abnormality was in the ipsilateral dorsolateral medulla oblongata at the level of the inferior olive. The jaw jerk, the most widely used brain stem reflex in clinical neurophysiology, had no apparent topodiagnostic value.

Touching the (edge of the) cornea with a wisp of cotton elicits bilateral blinking, the **corneal** or **blink reflex**. The **blink reflex** is an important reflex in clinical studies (see Ongerboer de Visser and Kuypers 1978; Ongerboer de Visser 1980; Aramideh et al. 1997; Aramideh and Ongerboer de Visser 2002; Cruccu et al. 2005). It consists of two responses, R1 and R2 (Fig. 6.29a): R1 is unilateral and R2 bilateral. The afferent limb of this multisynaptic reflex is formed by the ophthalmic division of the trigeminal nerve and the efferent one by the facial nerve. The central pathway, through which the blink reflex responses are mediated, includes the spinal trigeminal complex and the lateral tegmental field. The blink reflex can be interrupted by various types of brain stem lesions (see Fig. 6.29b and ▶ ***Clinical Case 6.9***).

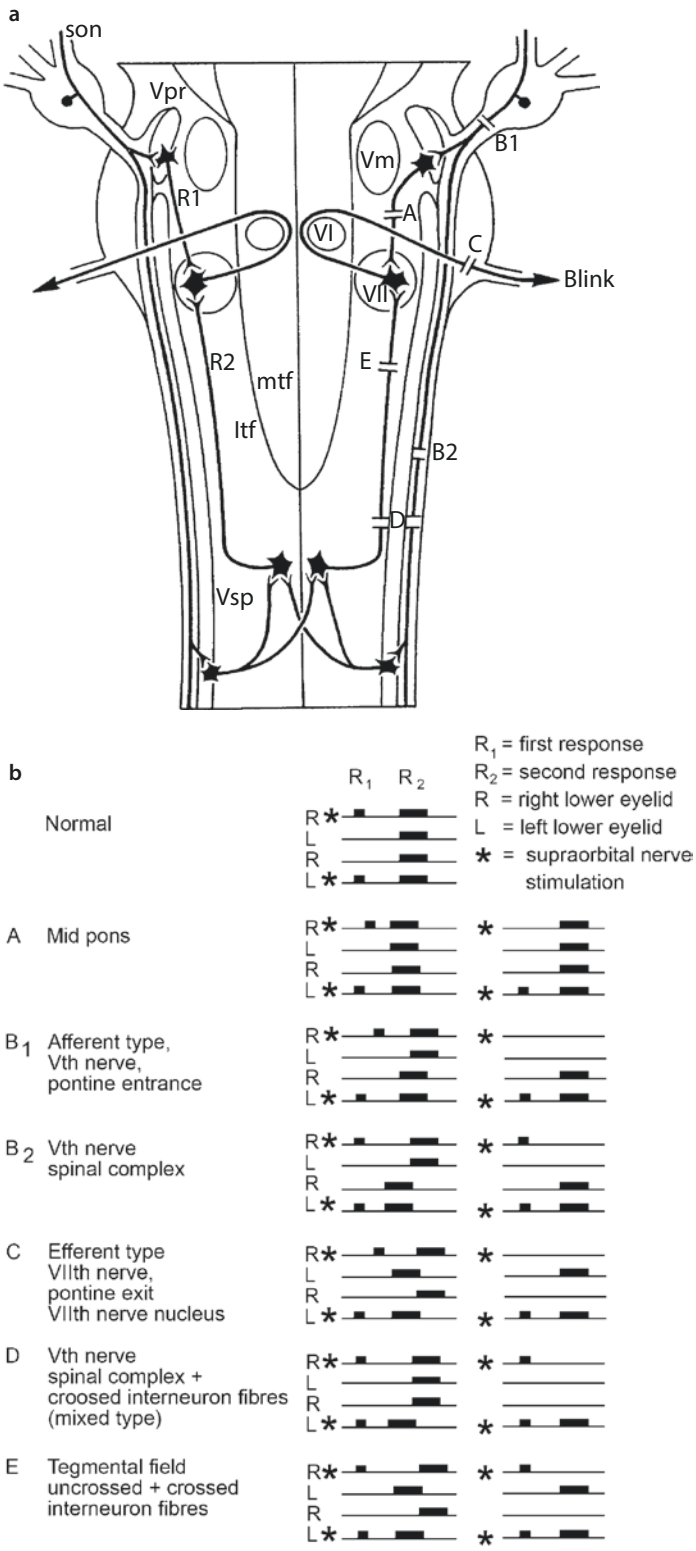

Fig. 6.29 **a** Diagram of the blink reflex and **b** R1 and R2 responses after various lesions of the blink circuit indicated by A–E. ltf, mtf lateral and medial tegmental fields, son supraorbital nerve, Vm motor trigeminal nucleus, Vpr principal sensory trigeminal nucleus, Vsp spinal trigeminal nucleus, VI abducens nucleus, VII facial nucleus. (After Aramideh et al. 1997)

Clinical Case 6.9 Late Blink Reflex Changes in Lateral Medullary Lesions

The blink reflex is an important reflex in clinical studies (see Ongerboer de Visser 1980; Aramideh et al. 1997; Cruccu et al. 2005). It consists of two responses, R1 and R2 (Fig. 6.29). R1 is **unilateral** and occurs at a latency of about 10 ms ipsilateral to the side of stimulation of the supraorbital nerve. The second or late response, R2, is **bilateral** and has a latency of some 30 ms. The common afferent limb of the reflex components is the ophthalmic division of the trigeminal nerve. The facial nerve is the common efferent limb. The central pathway, through which the blink reflex responses are mediated, includes the spinal trigeminal complex and the lateral tegmental field. Ongerboer de Visser and collaborators studied several cases of brain stem lesions involving late blink reflex changes (Ongerboer de Visser 1980; Aramideh et al. 1997; see **Case report**).

Case report: A 61-year-old hypertensive woman suddenly experienced diminished sensation of the left side of the body, followed by dysphagia and dysphonia. Physical examination revealed an alert woman with a blood pressure of 190/110 mm Hg and a regular pulse rate of 76/min. There was a right-sided Horner. The right corneal reflex response was absent after stimulation of either side, whereas a touch of the right or left cornea elicited a normal response in the left orbicularis oculi muscle. The strength of the facial muscles was normal on both sides. A paresis of the right soft palate was noted. No sensory deficits were found in the face, and vibration sense was normal on the left side. Other sensory modalities were disturbed in the limbs and trunk on the left side. Stimulation of the right supraorbital nerve, ipsilateral to the side of the lesion, elicited a normal ipsilateral R1 response with a latency of 10 ms and a normal contralateral R2 response with a latency of 30 ms (Fig. 6.30a), but no ipsilateral R2 response could be recorded. Stimulation of the left supraorbital nerve evoked normal ipsilateral R1 and R2 responses, but no contralateral R2 response could be elicited.

Seven months later, the patient died from a myocardial infarction. Autopsy showed an infarction in the right medullary lateral tegmental field between the inferior olive and the spinal trigeminal complex (Fig. 6.30b). Rostrally, the lesion extended slightly rostral to the inferior olive and caudally as far as the level of the crossing fibres of the medial lemniscus. The lesion included the caudal portion of the ambiguus nucleus and the spinothalamic tract.

In this patient as well as in the second case with a more caudal lesion reported by Aramideh et al. (1997), the R1 responses were normal. This type of "tegmental-type" R2 abnormality is likely due to a lesion of the lateral tegmental field, anywhere from the caudal medulla oblongata to the pontomedullary level (see Fig. 6.29), and is characterized by the absence of the R2 response ipsilateral to the lesion and a normal contralateral R2 response. In patients with this type of R2 response abnormality, the sensory modalities of the face and the strength of the facial muscles are normal.

Data for this case were kindly provided by Majid Aramideh (Department of Neurology, MCA Hospital, Alkmaar).

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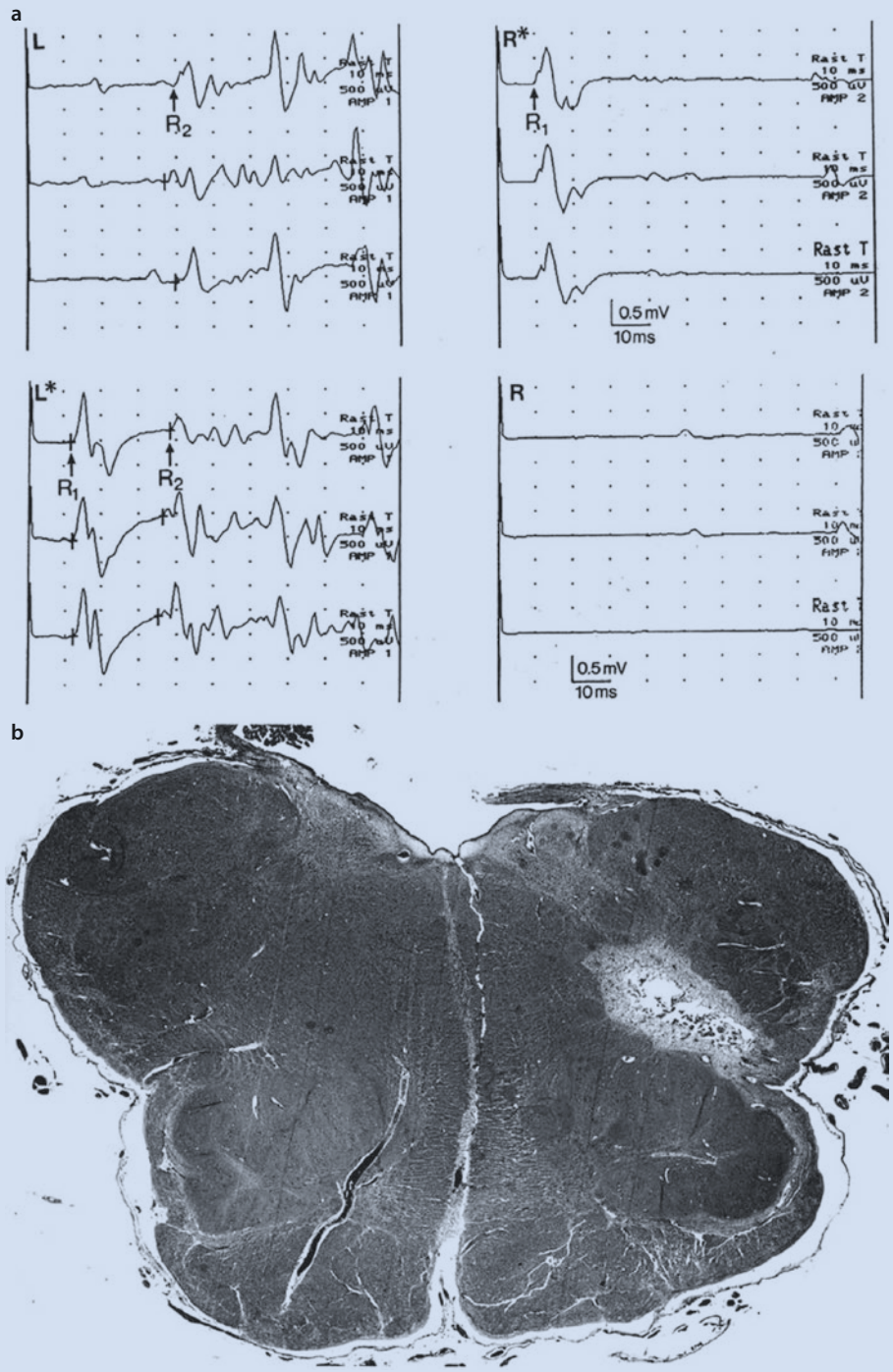


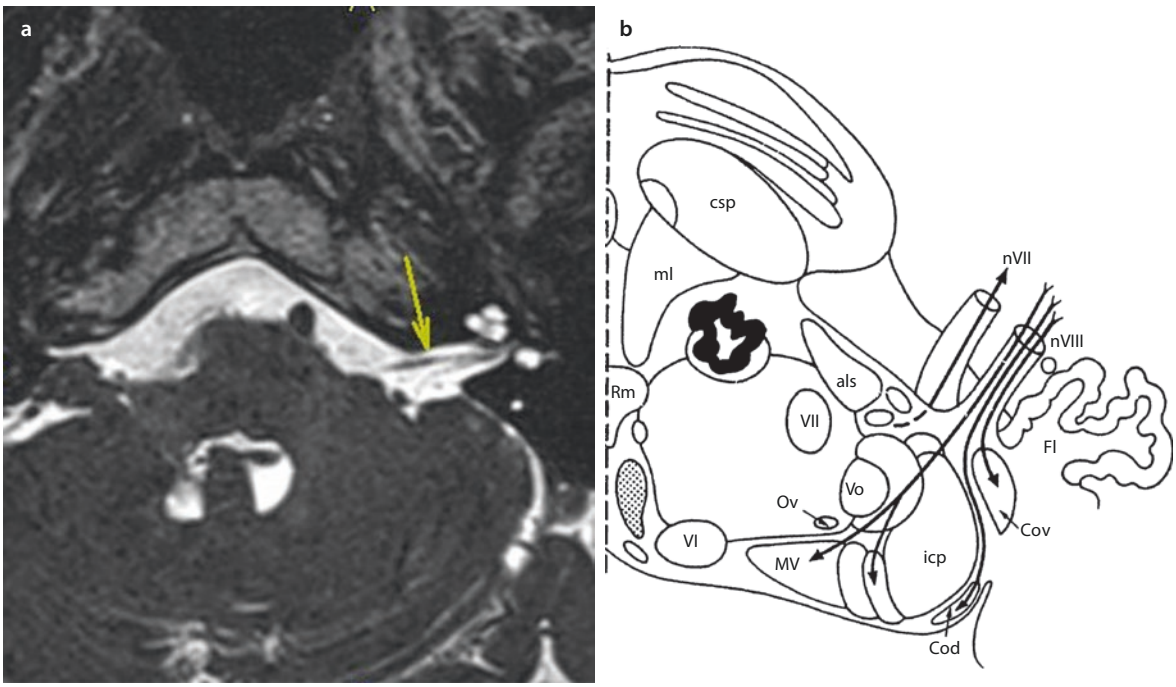
Fig. 6.30 **a** Blink reflexes in a patient with a right-sided lesion of the lateral medulla oblongata. The upper three pairs of traces represent reflex responses in the right (R) and left (L) orbicularis oculi muscles after stimulation of the right supraorbital nerve (R∗). No ipsilateral R2 response can be recorded on the right side after stimulation of the right supraorbital nerve. The ipsilateral right R1 response and contralateral left R2 responses are elicited normally. The lower three pairs of traces represent reflex responses in the left (L) and right (R) orbicularis oculi muscles after stimulation of the left supraorbital nerve (L∗). Normal ipsilateral R1 and R2 responses are recorded on the left side, whereas no contralateral right R2 response can be recorded after stimulation of the left supraorbital nerve. **b** LFB-stained section of the medulla oblongata showing an infarct in the lateral tegmental field between the inferior olivary nucleus and the spinal trigeminal nucleus. (From Aramideh et al. 1997; courtesy Majid Aramideh, Alkmaar; with permission from Oxford University Press)

6.6 The Facial Nerve

The **facial nerve** is a mixed nerve with several functions: (1) it is the motor nerve for facial expression; (2) its parasympathetic branches innervate the submandibular, sublingual and lingual glands as well as the lacrimal gland and glands of the palate and nasal cavity; and (3) it relays taste information from the anterior two-thirds of the tongue (see ▶ Sect. 6.7). The latter two components are also known as the **intermediate nerve** of Wrisberg. The exit of the facial nerve at the cerebellopontine angle is shown in ◘ Fig. 6.31. In clinical practice, a subdivision of the facial nerve into cisternal, meatal, labyrinthine, tympanic, pyramidal, mastoid and extracranial segments is used (Lang 1992). The facial nerve turns around the nucleus of the abducens nerve as the **genu of the facial nerve**, leaves the brain stem at the cerebellopontine angle, passes under the anterior inferior cerebellar artery (the **cisternal segment**) and enters the internal acoustic meatus with the vestibulocochlear nerve, where it directs as the **meatal segment** towards the facial area of the fundus of the internal acoustic meatus to enter the facial canal in the petrous part of the temporal bone. Here, the facial nerve bends twice; first the **labyrinthine segment** heads ventrolaterally, and then it turns as the **geniculum**, where the **geniculate ganglion** is found, travels dorsolaterally as the **tympanic segment**; then it turns again and descends caudalwards as the **mastoid segment** to leave the skull through the stylomastoid foramen. The **intracranial branches**, given off within the temporal bone, are (◘ Fig. 6.32) (1) the **greater petrosal nerve**, which arises in the geniculum, runs ventromedially within the bony canal, leaving it through the hiatus for the greater petrosal nerve, and joining the deep petrosal nerve to form the nerve of the pterygoid canal of Vidius to terminate in the pterygopalatine ganglion; (2) the **nerve to the stapedius muscle** from the mastoid segment; and (3) the **chorda tympani**, which also arises in the mastoid segment.

After emanating the intracranial branches, the facial nerve is now called the **proper facial nerve** or **extracranial segment**, which leaves the skull via the stylomastoid foramen, before entering the parotid gland, and gives off (◘ Fig. 6.32) (1) the **posterior auricular nerve**, which divides into an occipital branch for the occipital belly of the occipitofrontal muscle and an auricular branch for the temporoparietal and auricular muscles; (2) the **digastric branch** for the posterior belly of the digastric muscle; and (3) the **stylohyoid branch** for the stylohyoid muscle. Within the parotid gland, the proper facial nerve forms the **parotid plexus** and bifurcates into superior and inferior divisions. The **superior** or **temporofacial division** divides into temporal and zygomatic branches for the upper half of the facial muscles. The **inferior** or **cervicofacial division** divides into buccal, marginal mandibular and cervical branches for the lower half of the facial muscles.

The tortuous peripheral course of the facial nerve from the brain stem to the parotid gland is fairly constant, and, although several variations with clinical significance have been described, variation is the exception rather than the rule (Gasser and May 2000). ***Peripheral lesions*** of the ***facial nerve*** are discussed in ▶ Clinical Case 6.10 and ***congenital facial palsy*** in ▶ Clinical Case 6.11.



◘ **Fig. 6.31** **a** MRI and **b** corresponding horizontal section (after Duvernoy 1995), showing the exit of the facial nerve (*nVII*)

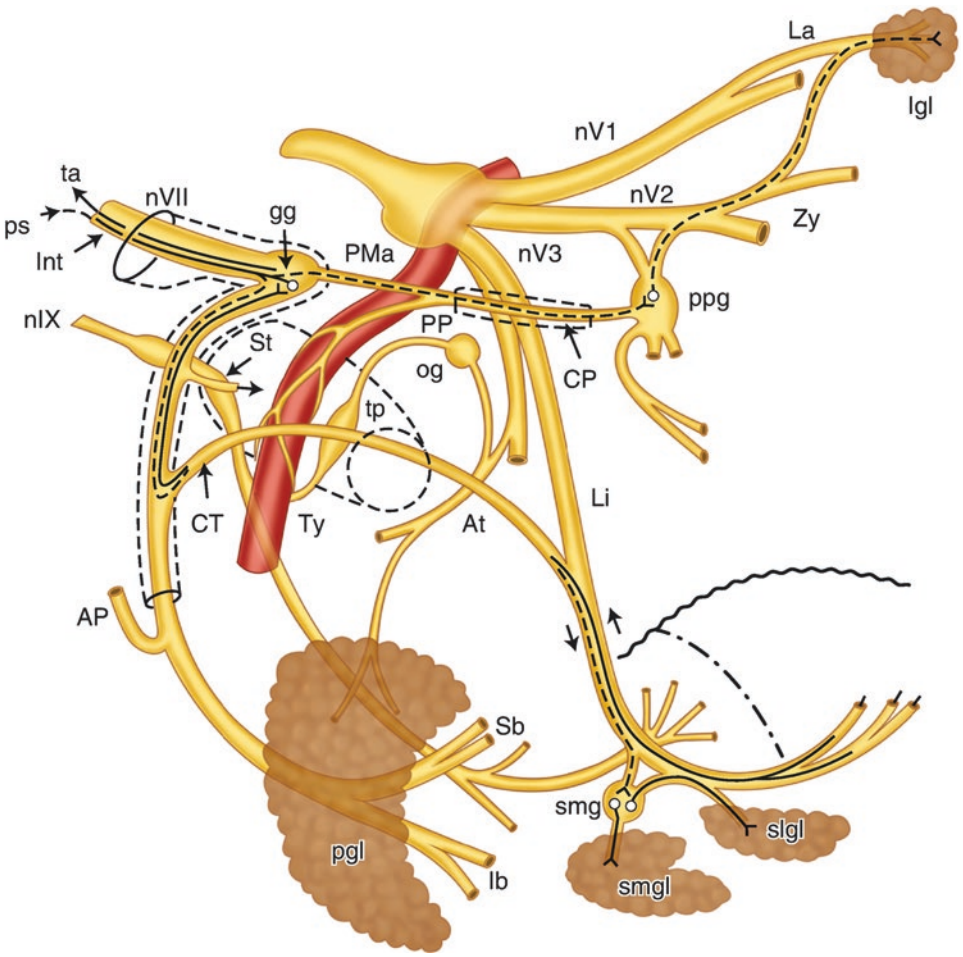


Fig. 6.32 Overview of the components of the facial nerve. AP posterior auricular nerve, At auriculotemporal nerve, CP pterygoid canal nerve, CT chorda tympani, gg ganglion geniculi, IB inferior branch of facial nerve, Int intermediate nerve, La lacrimal nerve, lgl lacrimal gland, Li lingual nerve, nV1 ophthalmic nerve, nV2 maxillary nerve, nV3 mandibular nerve, nVII facial nerve, nIX glossopharyngeal nerve, og otic ganglion, PMa petrosus major (greater petrosal) nerve, PP petrosus profundus (deep petrosal) nerve, ppg pterygopalatine ganglion, pgl parotid gland, ps parasympathetic fibres, SB superior branch of facial nerve, slg sublingual gland, smg submandibular ganglion, smgl submandibular gland, St stapedius nerve, ta taste afferents, tp tympanic plexus, Ty tympanic nerve, Zy zygomatic nerve. (After ten Donkelaar et al. 2007b; from ten Donkelaar et al. 2018)

In macaque monkeys, the **facial nucleus** can be divided into dorsal, intermediate, medial and lateral subdivisions, innervating the frontalis, orbicularis oculi, auricular and perioral muscles, respectively (Morecraft et al. 2001). In humans, the number of facial motoneurons is between 4500 and 9460 (van Buskirk 1945). In rhesus monkeys (*Macaca mulatta*), Morecraft et al. (2001) studied the **corticobulbar projections** to the facial nucleus. Although all cortical face representations innervate all nuclear subdivisions to some degree (see ► Chap. 9), the primary motor cortex (M1), the dorsal and ventral parts of the lateral premotor cortex and the caudal cingulate motor area all project primarily to the contralateral lateral subnucleus, which innervates the perioral muscles. The SMA (M2) projects bilaterally to the medial subnucleus, which supplies the auricular muscles. The rostral cingulate motor area projects bilaterally to the dorsal and intermediate subnuclei, which innervate the frontalis and orbicularis oculi muscles, respectively. These data indicate that the various cortical face representations may mediate different aspects of facial expression. Kuypers (1958b) studied the corticofacial projections in humans (see ► Chap. 9). In rats, Fay and Norgren (1997b) studied the premotor systems of facial motoneurons with the transneuronal tracer pseudorabies virus and found a pattern of innervation remarkably similar to that for trigeminal motoneurons (see ► Sect. 6.5). **Corticofacial projections** normally reach the facial motor nucleus at its location in the caudal pons. Occasionally, however, corticofacial fibres continue caudally and reach the facial nucleus via the medial lemniscus (Yamashita and Yamamoto 2001). In other cases, corticofacial fibres may course with the pyramidal tract to the medulla oblongata, cross the midline and ascend in the dorsolateral tegmentum to the facial nucleus (Urban et al. 2001a). A lesion after crossing of the corticofacial projections in the lateral medulla oblongata may explain the presence of an ipsilateral central facial paresis (Urban et al. 1998, 1999) or its occurrence in cases of Wallenberg syndrome (see ► Clinical Case 9.9).

Preganglionic parasympathetic fibres of the facial nerve arise in the **superior salivatory nucleus** and form two major branches: (1) the greater petrosal nerve for the lacrimal and nasal, palatine and nasopharyngeal glands (with postganglionic neurons in the pterygopalatine ganglion) and (2) the chorda tympani (with postganglionic neurons in the submandibular ganglion), which innervates all salivary glands, except the parotid gland.

Clinical Case 6.10 Facial Nerve Paralysis

Peripheral lesions of the ***facial nerve*** include the Bell palsy, the Ramsay Hunt syndrome and hemifacial spasm. ***Bell palsy*** is one of the most common neurological disorders. It consists of an acute paralysis often preceded by a history of aching pain in and around the ear on the day of onset. The palsy is usually complete at the onset, but recovery may be so rapid that the palsy appears incomplete by the time the patient is first seen. The prognosis is usually excellent; some 80% of the patients completely recover in 2 to 6 weeks. The aetiology of Bell palsy is thought to be a ***viral infection*** with damage to the swollen nerve caused by ***entrapment*** in the facial canal. In the ***Ramsay Hunt syndrome***, the facial nerve is damaged by the ***herpes zoster virus***. Very severe pain in the ear may precede the facial weakness by 24–26 hours with the later eruption of vesicles in or around the external auditory meatus or over the mastoid process. Other cranial nerves may also be involved, particularly the trigeminal nerve with sensory loss over the face and numbness of the palate due to a glossopharyngeal nerve lesion. The majority of patients recover to some extent but only 50% fully recover. ***Hemifacial spasm*** has many similarities to trigeminal neuralgia. Both are often caused by minor anatomical variations of blood vessels overlying the nerve. Hemifacial spasm consists of continuous twitching movements usually maximal around the eye and the mouth. The condition is often more annoying and embarrassing than unpleasant. It may occur at any age but is more commonly found in older age groups. Tumours at the cerebellopontine angle, basilar artery aneurysms and basal meningitis may all be responsible for this condition, but in most cases no definite cause is found. A case of a juvenile transient facial paralysis is shown as **Case report**.

Case report: An 8-year-old boy was wakening up in the morning with very mild paraesthesias in his right ear and a mild right-sided flaccid cheek (Fig. 6.33a). The paraly-

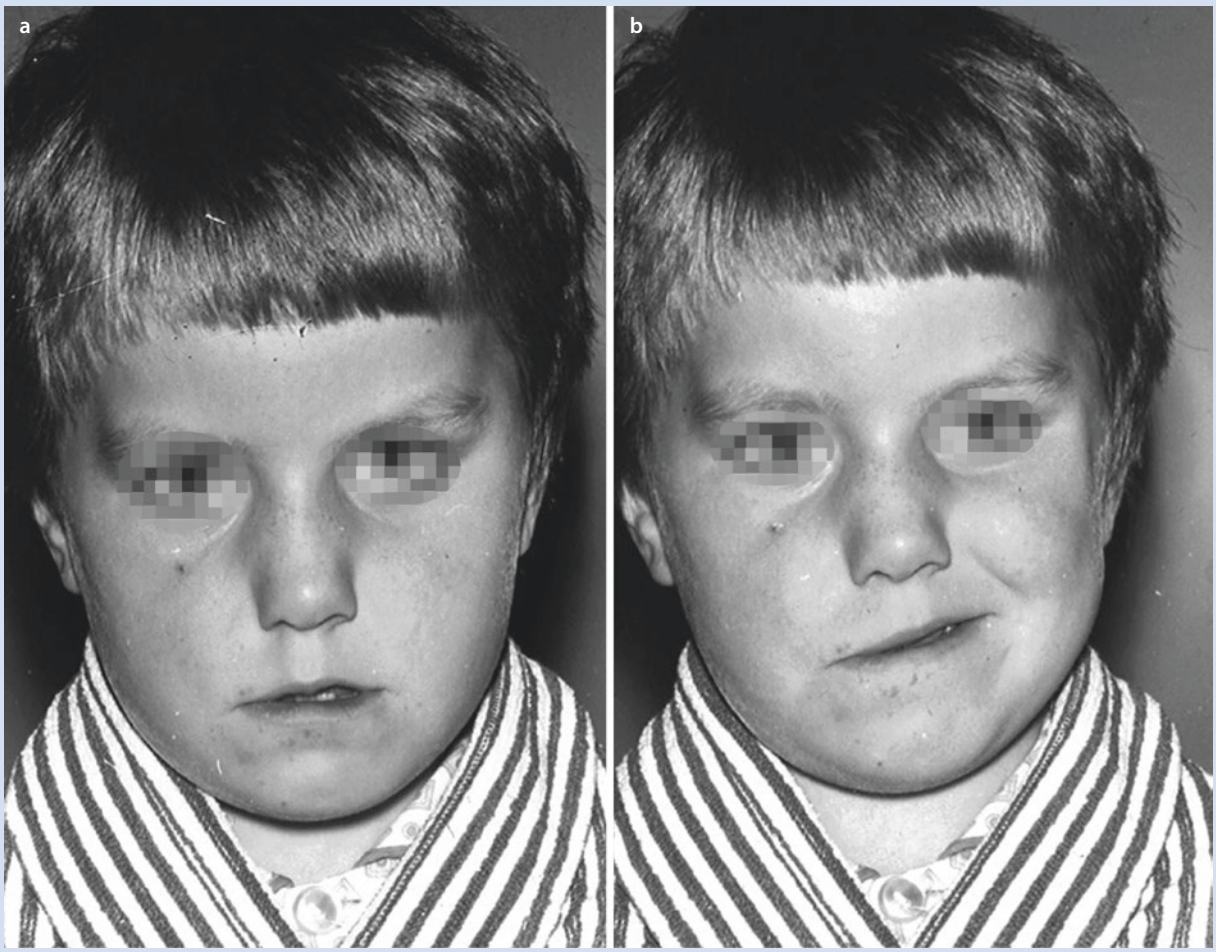


Fig. 6.33 A juvenile case of a transient peripheral facial paralysis: **a** mild right-sided flaccid cheek; **b** during smiling. (Courtesy Willy Renier, Kortrijk)

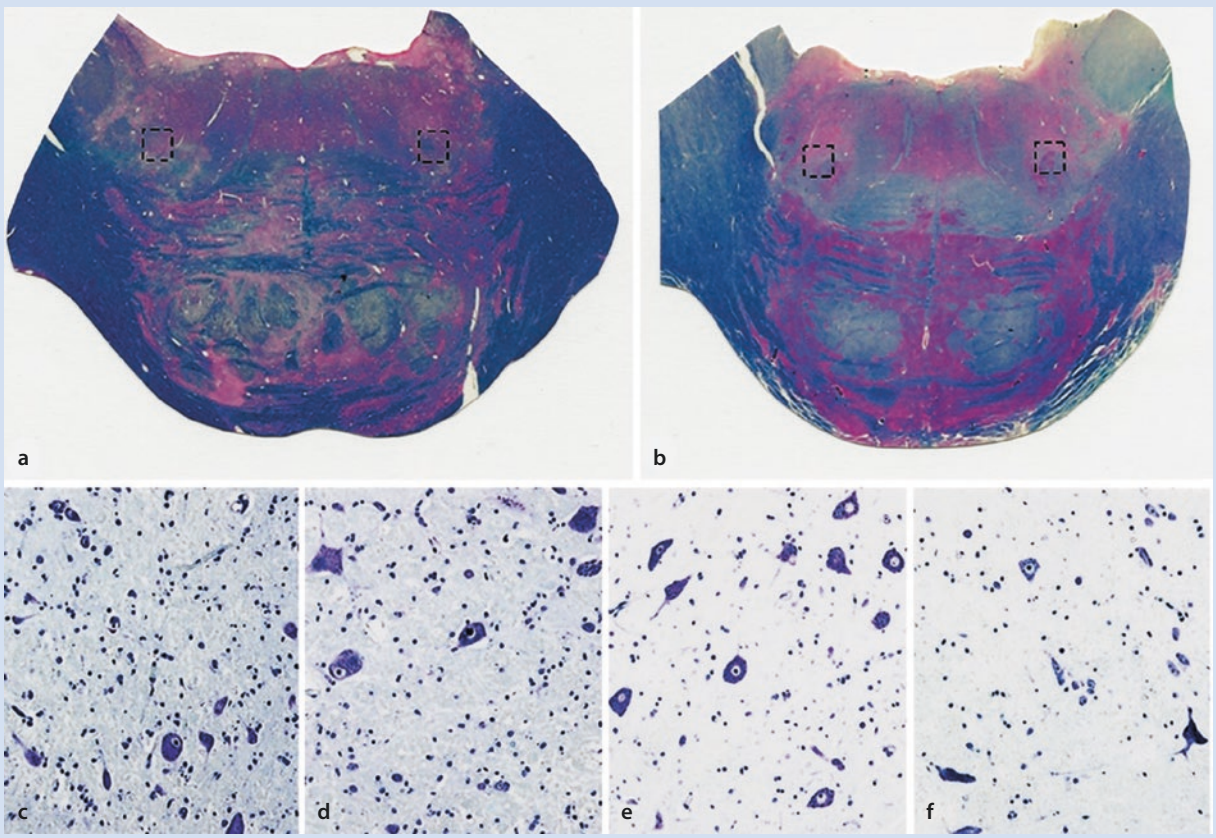
sis reached its maximum in a few hours. When trying to smile, his mouth was pulled to the opposite non-paralysed side (◘ Fig. 6.33b). Lacrimation was preserved but taste was reduced. There was no hyperacusis. After 10 days, the weakness spontaneously resolved within a week. Recovery was complete.

This case was kindly provided by Willy Renier (currently Kortrijk, Belgium).

Clinical Case 6.11 Congenital Facial Palsy

Neuropathological data on ***hereditary congenital facial palsy*** are scarce. Verzijl et al. (2005) described a marked decrease in the number of neurons in the facial nucleus in three members of a family with autosomal dominant congenital facial palsy (see **Case report**).

Case report: Brain stem pathology could be studied in three affected female members of a family with autosomal dominant, congenital, nonprogressive facial palsy linked to chromosome 3q (Kremer et al. 1996). Two of them, sisters, died at the ages of 88 and 86 years, respectively, owing to unspecific causes. The third patient, a granddaughter of the second patient, died suddenly because of an undiagnosed acute bacterial meningitis, at the age of 41 years. Patients 1 and 2 showed bilateral congenital facial paresis. In the first patient, the left side was more affected than the right side, whereas in the second patient, the right side was more affected than the left side. The third patient showed a congenital right-sided facial palsy. Data on the facial nuclei of one of the two sisters and of the granddaughter are shown in ◘ Fig. 6.34. The number of cells in each facial nucleus was estimated by counting the distinct nucleoli of facial motoneurons in every tenth 8-µm-thick, cresyl violet-stained section and by multiplying the number obtained by 10. The number of facial motoneurons clearly corresponded with the presence of ipsilateral or bilateral facial palsy and the grade of affection. The first case showed a bilateral decrease in the number of facial motoneurons, the left side (◘ Fig. 6.34c) being more affected



◘ **Fig. 6.34** Two related cases, an 88-year-old woman **a**, **c**, **d** and her 41-year-old granddaughter **b**, **e**, **f** with congenital facial paralysis: **a**, **b** sections through the pons with the level of the facial nuclei indicated; **c**, **d** details of the left and right facial nuclei in the first patient; **e**, **f** details of the left and right facial nuclei of her granddaughter. (From ten Donkelaar et al. 2014a)

than the right side (Fig. 6.34d). In the left facial nucleus, 520 motoneurons were estimated and in the right nucleus 950. In the second case, the right side was more affected: 960 motoneurons were estimated at the left side and 600 at the right side. In the third case with ipsilateral, right-sided facial palsy, in the right facial nucleus only 280 motoneurons were present (Fig. 6.34e), whereas in the left, apparently normally functioning nucleus 1680 neurons were estimated (Fig. 6.34f). In three age-matched controls, the number of neurons ranged between 5030 and 8700, comparable to van Buskirk's (1945) data obtained from 37 control cases (5400–9460 facial motoneurons, with a mean of 6811).

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6.7 The Gustatory System

The **peripheral gustatory apparatus** includes various types of taste buds on the dorsum of the tongue, the soft palate, the pharynx, the epiglottis and the larynx (see Pritchard and Norgren 2004; Pritchard 2012). On the rostral part of the human tongue, taste buds occur in the fungiform papillae, but most taste buds are located on the sides of the foliate papillae along the lateral margins of the tongue and in the trenches of the circumvallate papillae on the posterior part of the tongue (Fig. 6.35). In general, the chorda tympani branch of the facial nerve innervates the rostral two-thirds of the dorsum of the tongue, whereas the lingual branch of the glossopharyngeal nerve innervates the posterior one-third. Gustatory input from the palate and pharynx most likely travels via branches of the glossopharyngeal and vagus nerves.

Primary gustatory afferents project to the **nucleus of the solitary tract** (Beckstead and Norgren 1979; Satoda et al. 1996; see Fig. 6.36c), although often several, up to 10, nuclei may be distinguished (Törk et al. 1990; Paxinos and Huang 1995; Paxinos et al. 2012). These (sub)nuclei are not so obvious in the human brain stem (Büttner-Ennever and Horn 2014); therefore, the general term nucleus of the solitary tract will be used. In monkeys, axons of the intermediate nerve that innervate taste buds on the rostral part of the tongue and the soft palate terminate within the lateral part of the nucleus of the solitary tract. The glossopharyngeal nerve terminates within both the lateral and medial divisions of the rostral part of the nucleus of the solitary tract. The terminations of gustatory fibres passing via the VIIth, IXth and Xth cranial nerves overlap considerably. The terminal distributions of these nerves within the nucleus of the solitary tract suggest a subdivision of the nucleus into rostral (gustatory) and caudal (visceral) segments (Beckstead and Norgren 1979; Pritchard and Norgren 2004; Pritchard 2012). For the human brain stem, Olszewski and Baxter (1954) distinguished medial and lateral subdivisions as well as a rostral prefacial extension, termed the nucleus ovalis. Törk and collaborators subdivided the human nucleus of the solitary tract into ten subnuclei, of which at least one, the interstitial nucleus, contains gustatory neurons (Törk et al. 1990; McRitchie and Törk 1993). Of the human cases summarized by Pritchard and Norgren (2004), the case of Nageotte (1906) is the most informative. Postmortem examination of a patient with stomach cancer, who developed a right facial paralysis a month prior to death, revealed a metastasis in the facial canal just below the geniculate

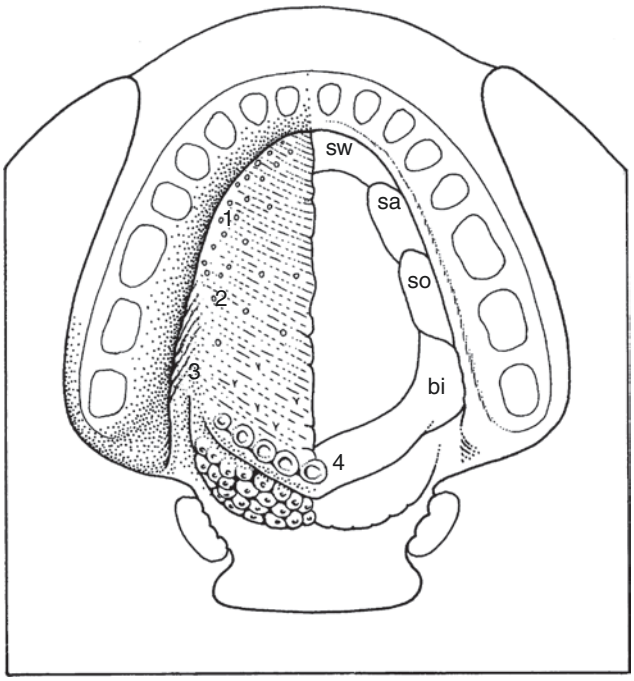


Fig. 6.35 The papillae of the peripheral gustatory apparatus shown on the dorsal surface of the tongue: on the left, the following types of papillae are shown: *1* filiform, *2* fungiform, *3* foliate and *4* vallate papillae; on the right the various taste qualities: bi bitter, sa salt, so sour and sw sweet. (After ten Donkelaar et al. 2007b)

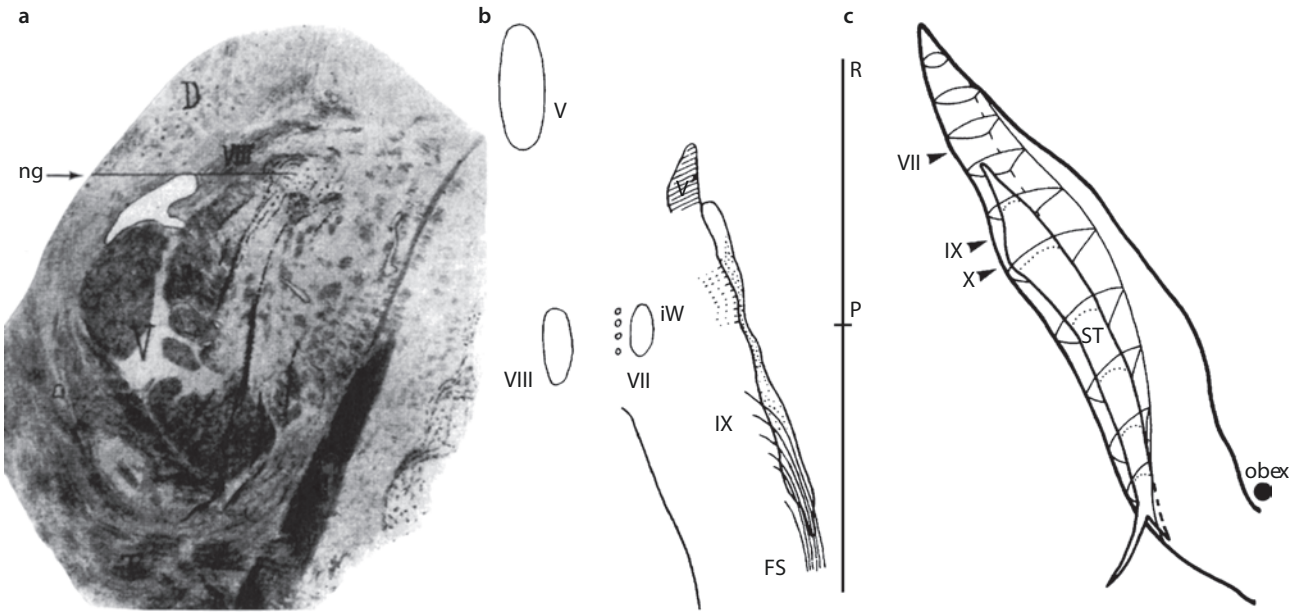


Fig. 6.36 **a, b** Nageotte's (1906) data on degenerating intracranial axons of the intermediate nerve (see text for further explanation). **c** Primary gustatory projections to the monkey nucleus of the solitary tract. (After Beckstead and Norgren 1979). ng nucleus or gelatinous substance of the solitary bundle, ST solitary tract, VII, IX and X cranial nerve input to nucleus of the solitary tract

ganglion. In Marchi material, Nageotte (1906) traced degenerating axons to what was then known as the nucleus or gelatinous substance of the solitary bundle (Fig. 6.36a, b), which is comparable to the nucleus ovalis of Olszewski and Baxter (1954) and the interstitial nucleus of McRitchie and Törk (1993).

In primates, **ascending gustatory projections** from the nucleus of the solitary tract reach the ventrobasal thalamus (Beckstead et al. 1980; Pritchard et al. 2000). Projections from the rostral, primarily gustatory, part of the nucleus of the solitary tract ascend in the ipsilateral central tegmental tract, bypass the parabrachial nucleus and terminate in the caudal half of the parvocellular division of the ventral posteromedial nucleus or VPMpc (Fig. 6.37) as distinguished by Olszewski (1952), for which Hirai and Jones (1989) suggested the term basal ventromedial nucleus (VMb). The parabrachial nucleus receives projections only from the caudal and commissural viscerosensory regions of the nucleus. The prepontine gustatory relay found in rodents (see Norgren 1995 for review) is either absent or attenuated in primates. Gustatory projections from the medulla, unlike most other sensory projections, are strictly ipsilateral. The few clinical studies available (Pritchard and Norgren 2004; Pritchard 2012) underline that in humans the ascending gustatory projections from the nucleus of the solitary tract pass ipsilaterally through the hindbrain. Ipsilateral taste deficits were described in patients with tegmental damage caused by haemorrhage or embolic infarction (Goto et al. 1983; Nakajima et al. 1983; Graham et al. 1988; Onoda and Ikeda 1999) or multiple sclerosis (Uesaka et al. 1998; Combarros et al. 2000), involving the central tegmental tract.

In primates, electrophysiological studies have shown the presence of gustatory neurons within the **thalamic gustatory relay**, i.e. the medial half of the VPMpc (Pritchard et al. 1986, 1989). In three awake thalamotomy patients, Lenz et al. (1997) electrically stimulated the posterior thalamus (the oral and caudal parts of the VPL as well as the VPMpc). In several instances, the patients reported taste sensations on the ipsilateral side of the tongue. The VPMpc projects primarily to the granular part of the posterior insula (the primary taste cortex; see Mesulam and Mufson 1982; Pritchard et al. 1986; Carmichael and Price 1995a, b; Pritchard 2012), which projects to nearby dysgranular and agranular regions of the insula (secondary taste cortices). Subsequent projections to the orbitofrontal cortex may provide the anatomical substrate for integration of taste with visual, auditory, olfactory, somatosensory and general visceral information (Pritchard and Norgren 2004; Pritchard 2012). Craig (2014, 2015) described the entire fundus of the insula under the posterior part of the circular sulcus as a continuous strip of granular cortex, called the **dorsal fundus of the insula** with distinct posterior (Idfp) and anterior (Idfa) halves. The coherent, topographic projections of the posterior part of the ventromedial nucleus (VMpo), receiving spinothalamic projections from lamina I neurons, and the basal ventromedial nucleus (VMb), receiving gustatory projections, to this cortical strip prompted its identification as **interoceptive cortex** (see ▶ Chaps. 4 and 15).

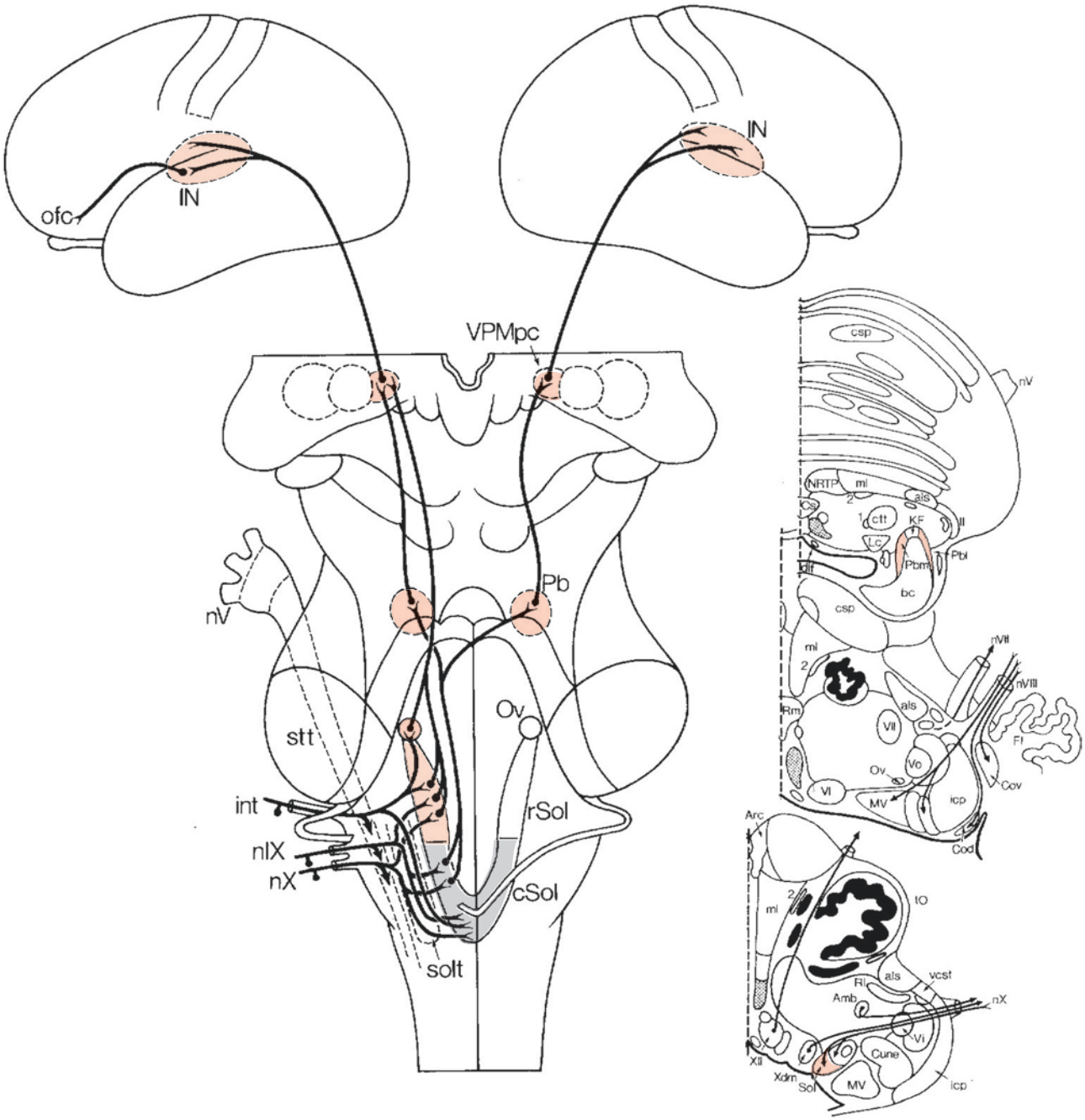


Fig. 6.37 The ascending gustatory system in primates (after Pritchard and Norgren 2004). Various brain stem nuclei are shown in horizontal sections of the human brain stem (after Duvernoy 1995). Gustatory centres such as the rostral part of the nucleus of the solitary tract are shown in *light red*, the caudal viscerosensory part of the nucleus of the solitary tract in *light grey*. cSol caudal part of solitary tract nucleus, IN insula, int intermediate nerve, nV trigeminal nerve, nIX glossopharyngeal nerve, nX vagus nerve, ofc orbitofrontal cortex, Ov oval nucleus, Pb parabrachial nucleus, rSol rostral part of solitary tract nucleus, solt solitary tract, stt spinal trigeminal tract, VPMpc parvocellular part of ventral posteromedial nucleus, *1* posterior or dorsal trigeminothalamic tract, *2* anterior or ventral trigeminothalamic tract, *3* rubrospinal tract, *4* habenulo-interpeduncular tract

The **gustatory cortex** was also demonstrated by mapping the evoked potentials produced by electrical stimulation of the chorda tympani and the lingual branch of the glossopharyngeal nerve, both in New World (Benjamin and Burton 1968; Benjamin et al. 1968) and Old World monkeys (Ogawa et al. 1985, 1989; Ito and Ogawa 1994). Rolls and co-workers demonstrated other gustatory neurons throughout the posterior orbitofrontal cortex (Rolls et al. 1990, 1996; Rolls and Bayliss 1994; Rolls 2012). In humans, Penfield and Faulk (1955) dem-

onstrated the participation of the insular cortex in taste during cortical stimulation carried out in awake patients during epilepsy surgery. Cascino and Karnes (1990) reported three patients who had ***gustatory aura*** together with tingling or numbness on one side of the body. All three had MRI evidence of lesions in the insula. **Human imaging studies** provided rather conflicting data. In some studies (Small et al. 1997, 1999; Barry et al. 2001; Small 2010; Veldhuizen et al. 2011), taste-evoked activity was found in only the ipsilateral insula, whereas in others bilateral effects were found (Kobayakawa et al. 1996, 1999; Faurion et al. 1999; Frey and Petrides 1999; King et al. 1999; O'Doherty et al. 2001). There is also disagreement about the rostrocaudal location of the primary taste cortex. PET and fMRI studies showed that gustatory stimuli activate parts of the orbitofrontal cortex (Zald et al. 1998; O'Doherty et al. 2001; Rolls 2012).

6.8 The Vestibulocochlear Nerve

The **vestibulocochlear nerve** emerges at the cerebellopontine angle caudal to the facial nerve (Fig. 6.38), then heads laterally into the lateral cerebellopontine cistern and continues into the cistern of the internal acoustic meatus in the bony acoustic meatus. Here, it divides into two divisions, the vestibular and cochlear nerves, which carry sensory impulses from the membranous labyrinth of the inner ear to the vestibular and cochlear nuclei. 3D-CT allows the visualization of the major components of the inner ear (Fig. 6.39). CT and high-resolution MR microscopy have improved the visualization of many components of the vestibular system (Lane et al. 2004, 2005; Gunny and Yousry 2007). The cochlear nerve and nuclei will be discussed in ▶ Chap. 7.

The **labyrinth** (Fig. 6.39) consists of the bony labyrinth, a set of passages in the skull, lined with membranes that contain endolymph and which form the membranous labyrinth. The **membranous labyrinth** consists of a large swelling, the **utricle**; a smaller one, the **saccule**; and three narrow **semicircular ducts** in the semicircular canals that emerge from the utricle. The semicircular canals are oriented orthogonal to each other: there are lateral or horizontal, anterior or superior, and posterior canals. The vestibular part of the membranous labyrinth is connected with the auditory part by a thin tube, the ductus reuniens. Each semicircular canal contains a sensory end-organ ridge or crest (the **ampullary crest**) that rests in a swelling near one end of the canal, the ampulla. Hair cells extend cilia from the ampullary crest

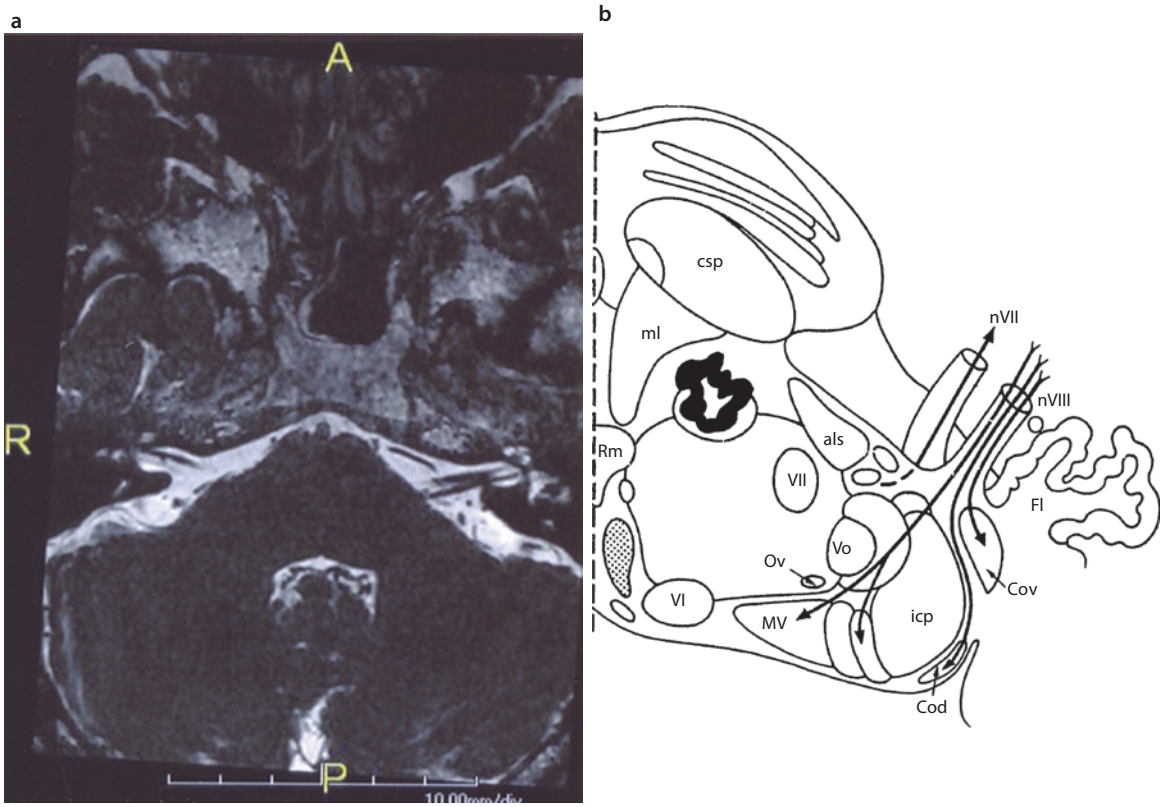


Fig. 6.38 **a** MRI and **b** corresponding horizontal section of the brain stem showing the entrance of the vestibulocochlear nerve (**b** based on Duvernoy 1995). At this level, the vestibulocochlear nerve (*nVIII*) terminates in the medial vestibular nucleus (*MV*) and the dorsal (*Cod*) and ventral (*Cov*) cochlear nuclei

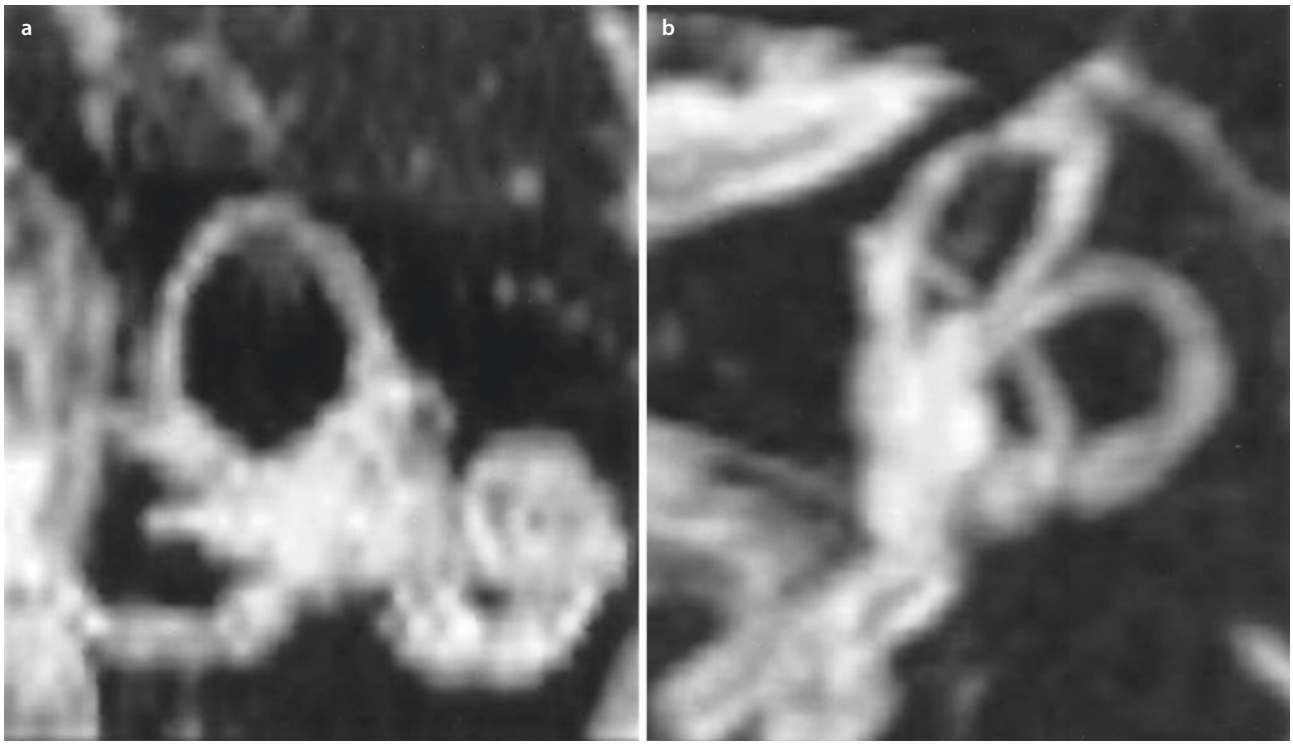


Fig. 6.39 **a**, **b** 3D-CT imaging anatomy of the vestibular system (courtesy Ton van der Vliet, Groningen)

into a gelatinous mass, the cupula, that occludes the canal passage. The hair cells contain many stereocilia and one kinocilium. Pressure of the endolymph on the cupula deflects the stereocilia. Their deflection towards the kinocilium depolarizes the hair cells, which make synaptic contacts with vestibular afferents. Semicircular canal afferents encode rotational velocity of the head as shown in squirrel monkeys (Fernandez and Goldberg 1971; Goldberg and Fernandez 1971). The utricle and the saccule each have a specialized area of sensory epithelium, the **macula** or **otolith organ**. The macula of the utricle is in the floor of the utricle, parallel with the base of the skull, whereas the macula of the saccule is vertically based on the medial wall of the saccule. The sensory epithelia of the two maculae contain hair cells among which are embedded small, dense particles, the otoliths. The hair cells are deformed and activated by head tilt and by linear acceleration of the head. The maculae thus respond to gravitational and linear acceleration (Fernandez et al. 1972; Fernandez and Goldberg 1976). The inner ear is vascularized by the labyrinthine artery, usually a branch of the anterior inferior cerebellar artery (Atkinson 1949; Kim et al. 1990; Schuknecht 1993). For vestibular function testing, see Brandt and Strupp (2005) and Wuyts et al. (2007).

The **vestibular nerve** transmits impulses from the maculae and ampullary crests for the sensation of balance. It is composed of superior and inferior parts (Fig. 6.40). The **superior part** or **utriculoampullary nerve** gives off three branches: (1) the **utricular nerve**, conveying information from the macula of the utricle; (2) the **anterior ampullary nerve**, conveying information of the ampullary crest of the anterior semicircular duct; and (3) the **lateral ampullary nerve**, conveying information from the ampullary crest of the lateral semicircular duct. The **inferior part** divides into two branches: (1) the **posterior ampullary nerve**, transmitting information from the ampullary crest of the posterior semicircular duct; and (2) the **saccular nerve**, transmitting information from the macula of the saccule.

6.8.1 The Vestibular Nerve and Nuclei

The vestibular nuclear complex senses the movement and position of the head in space. Signals are generated in the labyrinth of the inner ear. The ampullary crests of the three semicircular ducts respond to rotational acceleration of the head, and the maculae of the saccule and utricle respond to linear acceleration and gravity. This information is conveyed to the vestibular nuclei via the vestibular nerve and used to make compensatory eye and head movements as well as postural adjustments (Wilson and Melvill Jones 1979). Therefore, the vestibular nuclear complex has extensive connections with the ocular motor nuclei, the spinal cord and the cerebellum. The **primary vestibular afferent fibres**, arising from the primary vestibular neurons in the vestibular ganglion of

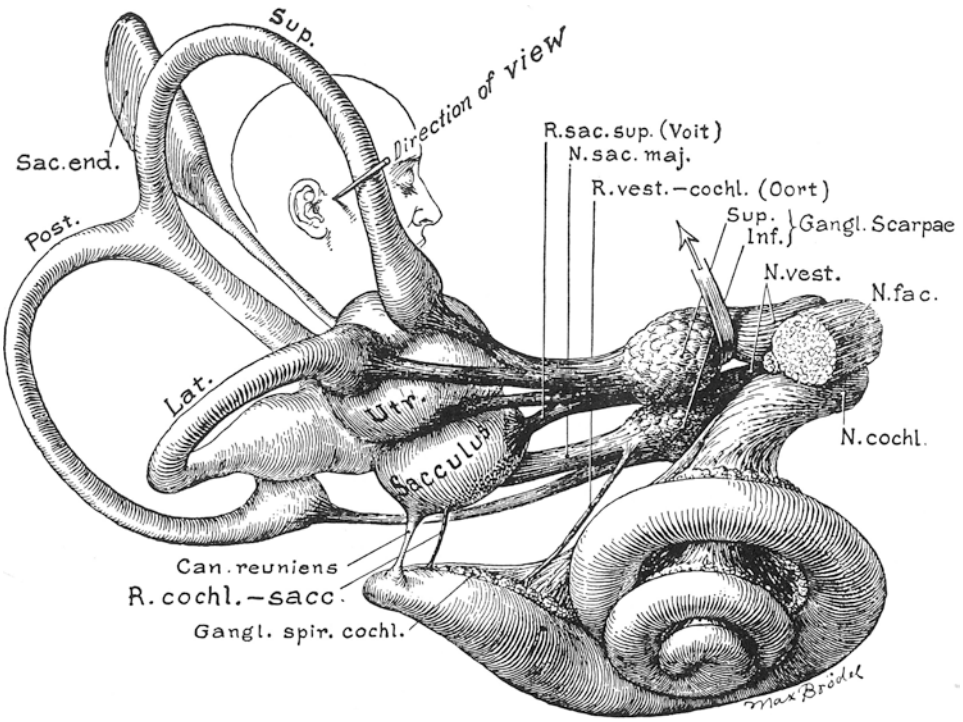


Fig. 6.40 The vestibulocochlear nerve and its branches (from Brödel 1946)

Scarpa, enter the brain stem at the level of the lateral vestibular nucleus (Carleton and Carpenter 1983, 1984; Carpenter and Cowie 1985a; Büttner-Ennever 1999). Almost all fibres bifurcate into a descending branch to the medial and inferior vestibular nuclei and an ascending branch to the superior vestibular nucleus and the cerebellum, particularly the anterior vermis and the nodulus and uvula (see ▶ Chap. 10). Fibres from the utricular macula reach primarily the inferior vestibular nucleus, with some terminals in the other vestibular nuclei (Imagawa et al. 1995). Saccular afferents give off terminal branches to the lateral and inferior vestibular nuclei (Imagawa et al. 1998). Most of the fibres from the semicircular canals end in the superior and medial vestibular nuclei. The inferior vestibular nucleus receives input from all parts of the vestibular labyrinth.

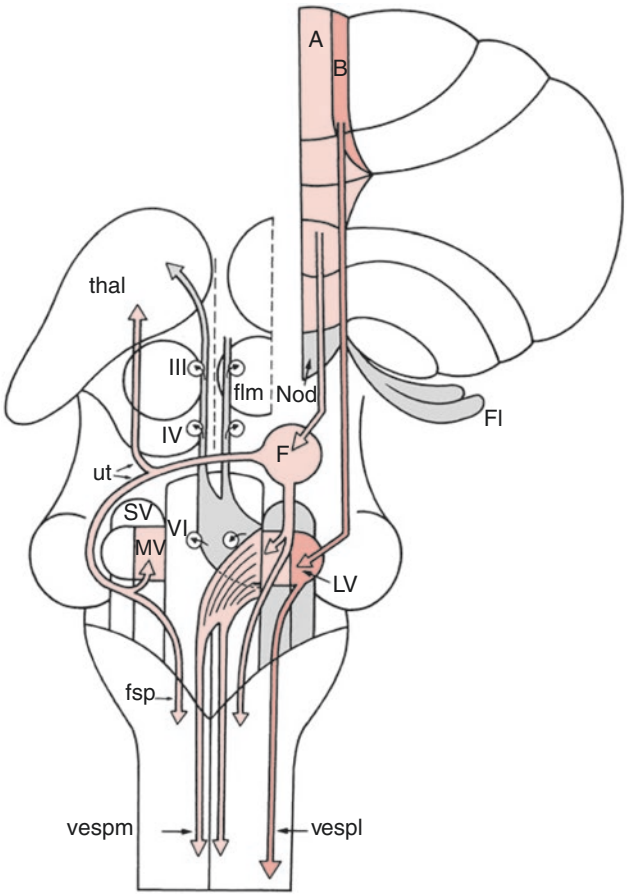
There are four major **vestibular nuclei**: the medial vestibular nucleus of Schwalbe, the lateral vestibular nucleus of Deiters, the inferior or descending vestibular nucleus and the superior vestibular nucleus of von Bechterew (Olszewski and Baxter 1954; Sadjadpour and Brodal 1968; Brodal 1984; Suárez et al. 1997; Büttner-Ennever and Gerrits 2004; Holstein 2012; Büttner-Ennever and Horn 2014). Additionally, there are several smaller accessory subgroups such as the interstitial nucleus and groups F (the magnocellular part of the inferior vestibular nucleus), L (the parvocellular part of the lateral vestibular nucleus) and Y (the marginal nucleus of the restiform body). The **medial vestibular nucleus** has the greatest volume and is the longest vestibular nucleus. Its rostral part is a major recipient of input from the semicircular ducts and innervates the ocular motor nuclei (McMasters et al. 1966; Carleton and Carpenter 1983; Carpenter and Cowie 1985a). Its caudal part projects via the medial vestibulospinal tract to the spinal cord, especially the cervical region, and is involved in vestibulocollic reflexes (see Wilson and Peterson 1988 and ▶ Chap. 9). Büttner-Ennever and Gerrits (2004) suggested a subdivision into magnocellular and parvocellular parts. The rostroventral part of the **lateral vestibular nucleus** receives projections from the cristae of the semicircular ducts and the macula of the utricle. It also participates in vestibulo-ocular reflexes, at least in part via the lateral vestibulothalamic tract (the ascending tract of Deiters). The lateral vestibular nucleus gives rise to the ipsilateral lateral vestibulospinal tract. The **inferior vestibular nucleus** also has vestibulo-oculomotor and vestibulospinal connections. The **superior vestibular nucleus** has mainly ascending projections via the superior cerebellar peduncle and a crossed ventral tegmental tract. Closely related to the medial vestibular nucleus is the **prepositus hypoglossi nucleus** (Brodal 1983; McCrea and Horn 2006), one of the perihypoglossal nuclei (see Büttner-Ennever and Horn 2014), all involved in eye movements. This nucleus lies medial to the medial vestibular nucleus and rostral to the hypoglossal nucleus beneath the floor of the fourth ventricle to the level of the abducens nucleus. It is thought to contribute to the maintenance of eye position or gaze in the horizontal plane (Baker and Berthoz 1975; McCrea and Horn 2006). The prepositus hypoglossi nucleus projects to the abducens nucleus (Langer

et al. 1986), the oculomotor nucleus (Graybiel and Hartwieg 1974; Steiger and Büttner-Ennever 1979), the vestibulocerebellum (Langer et al. 1985), the pontomedullary reticular formation and the superior colliculus.

6.8.2 Fibre Connections of the Vestibular Nuclei

The vestibular nuclear complex influences the motor system via its connections with the spinal cord (see ▶ Chap. 9), the cerebellum (see ▶ Chap. 10), the ocular motor nuclei and the thalamus. Several parallel pathways run from the vestibular nuclei to the ocular motor nuclei (◘ Fig. 6.41). The best studied of the **vestibulo-oculomotor pathways** is the three neuron arc, composed of the primary afferent canal afferents projecting to the vestibular nuclei, which in turn project to the motoneurons of the abducens, trochlear and oculomotor nuclei (Tarlov 1969, 1970; Carleton and Carpenter 1983; Carpenter and Cowie 1985b; McCrea et al. 1987a, b; Graf et al. 2002). The secondary vestibular neurons project to the ocular motor nuclei via the MLF, the superior cerebellar peduncle, a crossed ventral tegmental tract and the ipsilateral ascending tract of Deiters (see ▶ Sect. 6.4.2). Secondary vestibular neurons do not just excite or inhibit the motoneurons of one eye muscle but project to several pools of extraocular motoneurons and generate a particular conjugate eye movement, upward, downward, torsional or horizontal (Büttner-Ennever and Gerrits 2004; Holstein 2012; Horn and Adamczyk 2012). Ipsilateral pathways are inhibitory and contralateral pathways excitatory. In guinea pigs, Graf et al. (2002) used transneuronal labelling with rabies virus injected into the medial rectus muscle to show the entire network underlying and related to horizontal eye movements. Time-sequence labelling revealed distinct circuitries which involved the vestibulo-ocular reflex and saccade generation (brain stem circuitry), adaptive plasticity (cerebellar modules) and possibly motivation and navigation (limbic, hippocampal and cortical structures).

Vestibulothalamic projections have been demonstrated to end bilaterally in the oral part of the VPL and to a lesser extent in the VPI and the lateral central ventroposterior nucleus (Lang et al. 1979). An ipsilateral vestibulothalamic tract passes adjacent to the medial lemniscus (Zwergal et al. 2008). The thalamic nuclei innervate **vestibular cortical areas** such as the parietal areas 2v, 3a, 7a and 7b and the parieto-insular and retroinsular vestibular cortex (Guldin et al. 1992; Akbarian et al. 1993; Brandt et al. 1994; Guldin and Grüsser 1998). The parieto-insular vestibular cortex plays a central role in the cortical vestibular network (Grüsser et al. 1990a, b; Dieterich et al. 2005b; Eickhoff et al. 2006; Dieterich 2007).



◘ **Fig. 6.41** Efferent vestibular projections. Vestibulo-oculomotor and vestibulospinal projections as well as the cerebellar control of the vestibular nuclear complex (see Chap. 10) are shown. A, B longitudinal cortical cerebellar projection zones, F fastigial nucleus, Fl flocculus, flm fasciculus longitudinalis medialis, fsp fastigiospinal fibres, LV, MV, SV lateral, medial and superior vestibular nuclei, Nod nodulus, thal thalamus, ut uncinate tract, vespl vespm lateral and medial vestibulospinal tracts, III, IV, VI oculomotor, trochlear and abducens nuclei. (After ten Donkelaar et al. 2007a)

6.8.3 Functional and Pathophysiological Aspects of Vestibular Control

Vestibular signals act on neck, trunk and limb muscles, as well as on the muscles moving the eye. **Vestibulocollic** and **vestibulospinal reflexes** make use of semicircular canal and otolith signals to stabilize the posture of the head and body. Their importance is demonstrated by damage to the labyrinth or the VIIIth nerve or by mechanical blockage of the semicircular canals. ***Unilateral labyrinthectomy*** causes an initial postural disability in which subjects lean or fall towards the side of the lesion (Smith and Curthoys 1989; Curthoys and Halmagyi 1995). Bilateral symmetrical plugging of the semicircular canals in cats, which removes head velocity signals with little loss of or imbalance in tonic vestibular nerve

activity, produces severe head instability with oscillations that may persist for several days (Baker et al. 1982).

Control of posture involves many levels within the nervous system. Therefore, ***disorders of posture*** can result from damage to the sensory periphery or to the forebrain, cerebellum, brain stem and spinal centres (see ▶ Chap. 9). Many of the more plainly visible postural disorders stem from damage to or diseases of the vestibular system such as vestibular neuritis, peripheral and central tumours or infarction and the Ménière syndrome (see ▶ Clinical Case 6.12). The most obvious form of vestibular system damage is unilateral labyrinthectomy, either performed experimentally in animals or caused by disease or surgical intervention against disease in humans (Wilson and Melvill Jones 1979; Peterson and Richmond 1988; Smith and Curthoys 1989; Hirose and Halmagyi 1996; Baloh and Honrubia 2001; Luxon and Bamiou 2007). The postural symptoms that appear immediately after the loss of vestibular input to one side of the brain vary across species. Translating or tilting platforms provide a means for assessing vestibular damage from unilateral labyrinthectomy or other sources, including those that result in total vestibular loss (Keshner et al. 1987; Allum et al. 1994). Patients with chronic bilateral loss may perform well on posture platforms when visual and somatosensory cues are present, but they fail completely to maintain an upright stance when the support surface and visual surround are both sway-referenced, so that only vestibular information is accurate. In contrast, patients with acute bilateral vestibular loss or patients who have not yet compensated for vestibular loss perform poorly on a posture platform if either vision or somatic sensation is sway-referenced. ***Vestibular neuritis*** may be caused by a latent infection of the vestibular ganglia with herpes simplex virus-1 (Brandt et al. 2005). The virus induces a vestibular tonus imbalance, causing acute onset of sustained rotatory vertigo, horizontal rotational spontaneous nystagmus towards the unaffected ear, postural imbalance with ipsilateral falls and nausea (see ▶ Clinical Case 6.12).

The **vestibulo-ocular reflex** (**VOR**) may be tested by caloric irrigation of the external auditory meatus. This manoeuvre induces the endolymph to circulate and therefore generates the stimulation of the hair cells of the semicircular ducts. As a rule of thumb, the normal reaction is the nystagmus' fast component being directed towards the side of stimulation in case of warm fluid perfusion and towards the contralateral side in case of cold fluid perfusion ("the nystagmus fleeing the cold"). A clinically important source of the occurrence of nystagmus, apart from peripheral vestibular causes, is the presence of structural lesions in the brain stem and cerebellum.

Central vestibular disorders are associated with demyelination, degeneration, vascular events or trauma and are usually accompanied by disequilibrium, nausea and eye movement disorders. Vertigo is much more common in peripheral vestibular disorders than in central disorders. The following central vestibular disorders may be distinguished (Baloh and Honrubia 2001; Luxon and Bamiou 2007):

1. ***Vertebrobasilar transient ischaemic attacks***, characterized by brief episodes of vertigo associated with one or more brain stem symptoms and signs characteristic for ischaemia of the posterior circulation; the commonest cause is atherosclerosis of the subclavian, vertebral and/or basilar arteries.
2. ***Lateral medullary infarction*** (***Wallenberg syndrome***).
3. ***Ischaemia*** in the territory of the anterior inferior cerebellar artery (AICA) may result in infarction in the dorsolateral pontomedullary region and the anteroinferior cerebellum (Osis and Baloh 1992). Since in about 85% of cases the labyrinthine artery arises from the AICA, there is usually also infarction of the membranous labyrinth, which results in both peripheral and central vestibular damages.
4. ***Cerebellar infarction or haemorrhage***.
5. ***Posterior fossa tumours***, in 50% of which vestibular and cochlear symptoms occur (Hirose and Halmagyi 1996).
6. ***Multiple sclerosis***, often associated with imbalance (Williams et al. 1997).

Vestibular brain stem syndromes are classified according to the three planes of the vestibulo-ocular reflex (Dieterich and Brandt 2001): the **pitch** (the sagittal plane), **roll** (the frontal plane) and **yaw** (the horizontal plane) planes. ***Vestibular nuclear lesions*** due to infarction of the lateral medulla oblongata (Wallenberg syndrome) cause a central vestibular disorder that affects the medial vestibular nucleus and possibly also the superior vestibular nucleus (Dieterich and Brandt 2001, 2008; Brandt et al. 2005). Caloric irrigation of the ears in Wallenberg patients elicited asymmetrical activations at the cortical level: caloric irrigation of the ear ipsilateral to the lesion caused no or a significantly reduced activation in the contralateral hemisphere, but in the ipsilateral hemisphere activation seemed normal (Dieterich et al. 2005a; Dieterich and Brandt 2008). Apparently, the crossed ascending fibres from the medial vestibular nucleus via the contralateral MLF were lesioned, and the ipsilateral vestibular thalamocortical projection from the superior vestibular nucleus was spared.

Unilateral lesions of the ***posterolateral thalamus*** cause an imbalance of vestibular tonus that results in perceptual disturbances and an imbalance of stance and gait with lateral falls but without oculomotor disorders (Dieterich and Brandt 1993; Brandt et al. 2005). In PET studies, Dieterich et al. (2005b; Dieterich and

Brandt 2008) showed that activation of the multisensory vestibular cortex was significantly reduced in the ipsilateral hemisphere if the ear ipsilateral to the thalamic lesion was stimulated, but less reduced in the hemisphere contralateral to the irrigated ear (see ▶ Clinical Case 6.13).

Vertigo may be defined as an unpleasant distortion of static gravitational orientation or an erroneous perception of motion of either the sufferer or the environment (Dieterich and Brandt 2001). Most of the central vestibular syndromes and some of the peripheral vestibular syndromes have a vascular origin (Dieterich and Brandt 2001; Brandt et al. 2005). Ischaemia may produce a combination of central and peripheral syndromes, as in AICA infarctions, the territory of which encompasses the labyrinth, tegmental and cerebellar structures (Atkinson 1949; Kim et al. 1990; Schuknecht 1993).

Clinical Case 6.12 Peripheral Vestibular Disorders

Common ***peripheral vestibular disorders*** include (Strupp and Brandt 1999; Brandt et al. 2005; Luxon and Bamiou 2007):

1. ***Acute vestibular neuritis***: Single episodes of acute rotational vertigo associated with nausea and vomiting, with or without cochlear symptoms, are common in all age groups. The attacks are thought to be due to a viral infection.
2. The ***Ramsay Hunt syndrome***, the clinical presentation of ***herpes zoster oticus*** with facial palsy, auricular rash and hearing loss, often associated with acute vertigo.
3. ***Ménière's disease***: Ménière's disease remains a clinical diagnosis characterized by fluctuating hearing loss, tinnitus and vertigo, often associated with sensations of fullness or blockage in the ear. The first attack most commonly occurs between the ages of 30 and 60. In about 60% of the affected, both vestibular and cochlear symptoms develop within 6 months of the onset of the disease. The course of Ménière's disease is variable, but in general there are clusters of episodes with attack-free periods that may last several years. Other patients, however, have a more progressive course with ultimate loss of auditory and vestibular functions. Bilateral involvement occurs in 20–50% of cases. Electrocochleography with transsynaptic recording at the promontorium is the most sensitive and specific test with broadening of the summating potential/action potential ratio. The underlying pathophysiology of Ménière's disease is thought to be ***endolymphatic hydrops***.
4. ***Migrainous vertigo***.
5. ***Benign positional paroxysmal vertigo***, the most common cause of vertigo in adults (see **Case report**). Schuknecht (1962) defined degenerative changes in the superior part of the vestibular nerve, the utricle and the horizontal and anterior semicircular ducts in such patients. Later, he identified basophilic deposits on the cupulae of the posterior semicircular canals and suggested the term ***cupulolithiasis*** for the mechanism giving rise to positional nystagmus of the paroxysmal type (Schuknecht 1969). Hall et al. (1979), however, found free-floating debris from the otolith organs moving within the posterior semicircular duct (canalithiasis).
6. ***Autoimmune inner ear disease***.
7. ***Labyrinthine trauma***.

Case report: A 54-year-old female suddenly experienced dizziness in the morning. The environment around her was spinning, and she was not feeling well but did not vomit. She did not experience tinnitus or otalgia at that moment. The dizziness usually occurred when she was just waking up and turned around in bed to get up. After a minute or so, these symptoms disappeared and she was feeling well again. At first, this occurred only sometimes in the morning; later on these attacks also occurred during the day, for instance, when hanging up washing on a washing line or taking something from the top shelf. Further questioning revealed that she fell off her bike a few weeks ago; she was not injured, but the attacks started since then. Physical examination showed normal tympanic membranes at both sides and normal hearing. When the patient was tested with the Dix Hallpike manoeuvre, positional nystagmus of the paroxysmal type was seen. The nystagmus appeared after a latency time of a few seconds and was short (less than 1 minute), rotatory, upbeat and came to an end. This ending of the nystagmus was the starting point of therapy for this dizziness with a benign clinical course. The goal of treatment is to move back the free-floating debris (canalithiasis) into a position where it will no longer cause vertigo, i.e. from the posterior semicircular duct towards the utricle. Several techniques are available to establish this result (◘ Fig. 6.42):

1. The Epley canalith repositioning manoevre (Hilton and Pinder 2008): the first step is to ask the patient to sit right up at the end of a table (◘ Fig. 6.42a). In the second step, the patient is laid down on its back with the head tilted back over the edge of the table and turned to one side. The third step includes slowly rotating the head towards the other side and finally (the fourth step) tilting the whole body and head over, until the patient is almost facing the floor. In the end, the fifth step, the patient is brought back up into a sitting position.

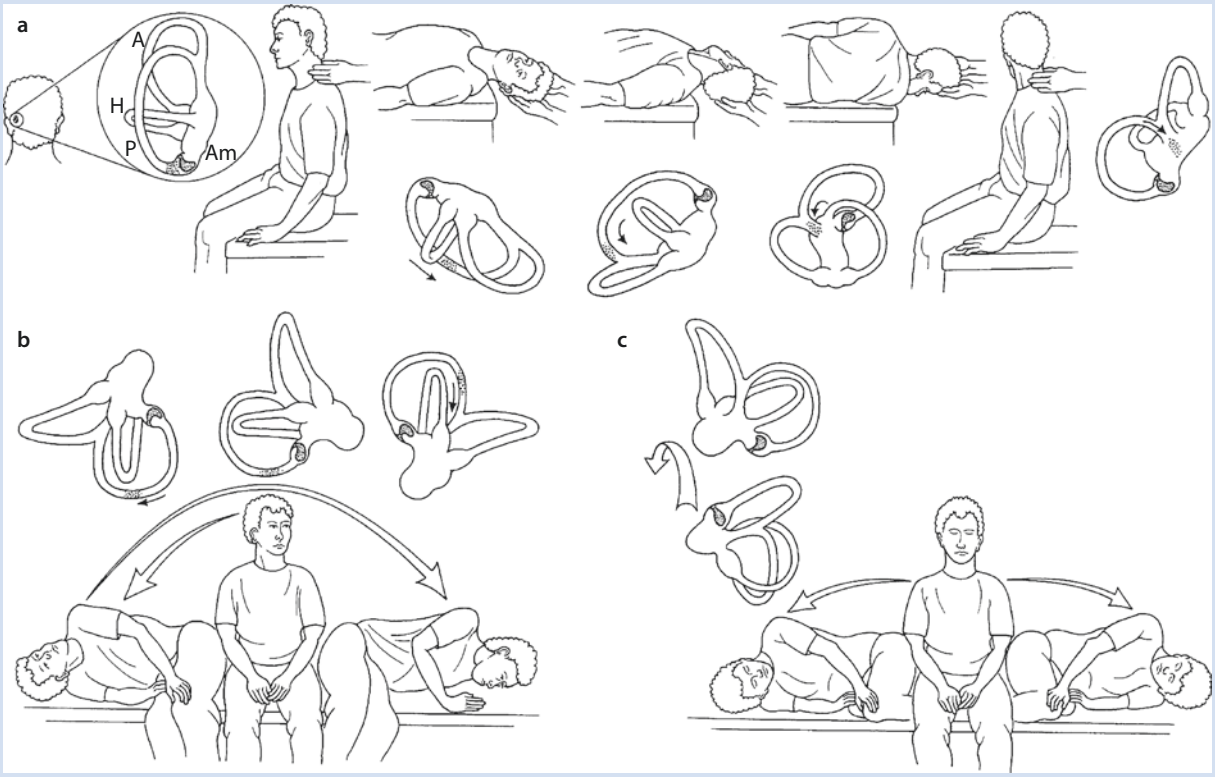


Fig. 6.42 Techniques to move back free-floating debris (*small dots*) in the posterior semicircular duct towards the utricle after Epley **a**, Semont **b** and Brandt-Daroff (**c**; after various sources; see text for explanation). A, H and P are the anterior (or superior), horizontal and posterior semicircular ducts and Am the ampulla of the utricle

2. The Semont manoeuvre relies on inertia, and therefore the transition from one ear to the other must be made very quickly (Fig. 6.42b).
3. The Brandt-Daroff exercises, a sequence of repetitive positioning (Fig. 6.42c).

Subjective improvement is achieved in around 90% of the patients. It is important to realize the benign course (Richard et al. 2005). In this case, the patient was relieved from her dizziness after the Epley manoeuvre was performed.

This case was kindly provided by Myrthe Hol (Department of Otorhinolaryngology, Radboud University Medical Centre, Nijmegen).

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Clinical Case 6.13 Central Vestibular Disorders

Dieterich and Brandt extensively studied central vestibular disorders (Dieterich et al. 2005; Dieterich and Brandt 2008). Some of their data are summarized in the **Case report**.

Case report: In ◘ Fig. 6.43, data based on fMRI studies in healthy volunteers versus left and right thalamic lesions are presented. Patients with posterolateral thalamic infarcts showed significantly reduced activation of the multisensory vestibular cortex in the ipsilateral hemisphere, if the ear ipsilateral to the thalamic lesion is stimulated. Activation of similar areas in the contralateral hemisphere is also diminished but to a lesser extent. These data show the importance of the posterolateral thalamus as a relay for vestibular information to the cerebral cortex.

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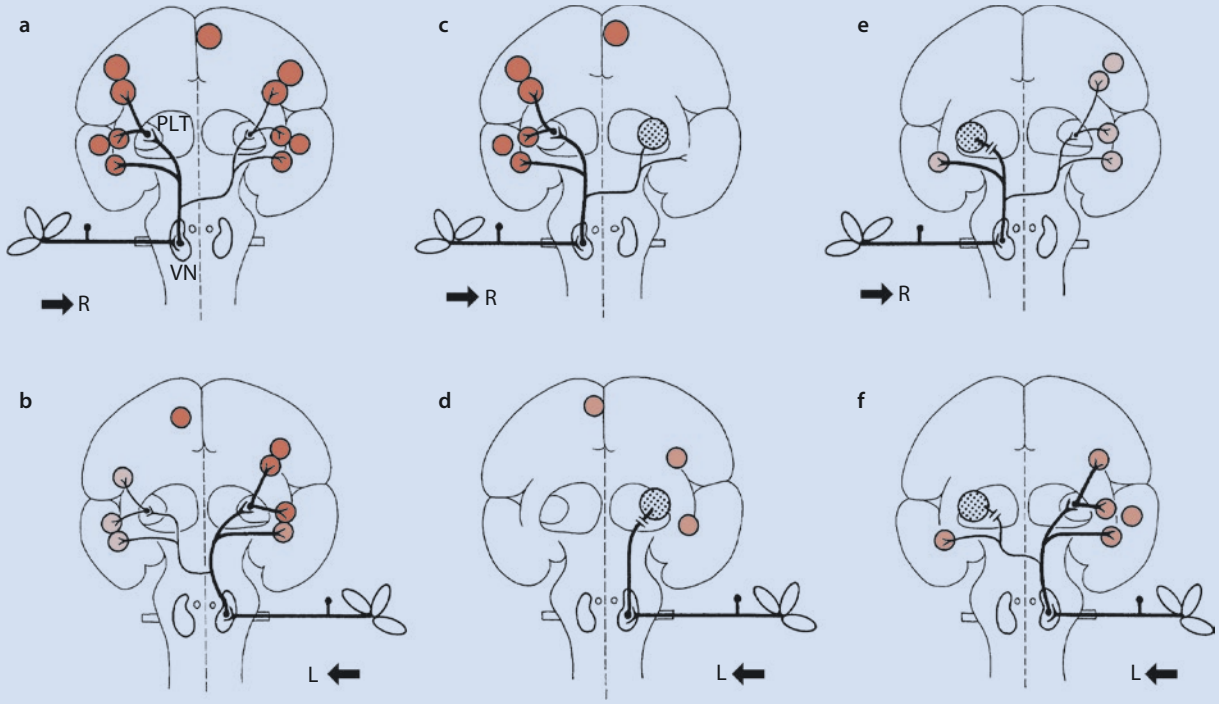

◘ **Fig. 6.43** Caloric irrigation of the right (*R*, above) and left (*L*, below) ear in healthy volunteers **a**, **b**, a left-sided thalamic lesion **c**, **d** and a right-sided thalamic lesion **e**, **f**. The activated nuclei are shown in various grades of *red* as found by fMRI and those that are not by *small dots*. (After Dieterich et al. 2005b and Dieterich and Brandt 2008). PLT posterolateral thalamic nucleus, VN vestibular nuclei

6.9 The Glossopharyngeal, Vagus and Accessory Cranial Nerves

6.9.1 The IXth, Xth and XIth Cranial Nerves

The glossopharyngeal nerve, the vagus nerve and the cranial root of the accessory nerve all leave the dorsal part of the medulla oblongata (Fig. 6.44). The **accessory nerve** is usually described as having two roots, a cranial and a spinal, which fuse in the jugular foramen to form a single nerve trunk. This trunk gives rise to an **internal branch**, joining the vagus nerve, and an **external branch**, representing the accessory nerve proper (Fig. 6.45). The latter is a purely efferent nerve and supplies the sternocleidomastoid and trapezius muscles. The cranial root fibres arise mainly from the ambiguus nucleus, form the internal branch, and may be viewed as an aberrant vagus rootlet.

The **glossopharyngeal** and **vagus nerves** are anatomically and functionally closely related (Fig. 6.45). The two nerves contain branchiomotor fibres originating in the **ambiguus nucleus**, parasympathetic fibres arising in the **inferior salivatory nucleus** and the **posterior** or **dorsal nucleus of the vagus nerve** and viscerosensory fibres. Viscerosensory fibres of the glossopharyngeal nerve come from the posterior third of the tongue, pharynx, soft palate, tonsils and tympanic cavity and have their cell bodies in the inferior ganglion. It leaves the skull through the jugular foramen where it contains two ganglia: (1) the **superior ganglion** of Ehrenritter in the foramen and (2) the **inferior** or **petrosal ganglion** of Andersch just below it. During its course through the neck, it gives off the following branches: (1) the stylopharyngeal branch for the stylopharyngeus muscle; (2) the tympanic nerve, which passes through the inferior tympanic canaliculus to the tympanic cavity, where it divides into branches for the tympanic plexus of Jacobson, supplying the mucosa, and continues as the lesser petrosal nerve to the otic ganglion; (3) a tubal branch for the mucosa of the auditory tube; (4) the carotid sinus nerve of Hering for the carotid body and the carotid sinus; (5) pharyngeal branches to the pharyngeal plexus; (6) tonsillar branches to the palatine tonsil and its surrounding mucosa; and (7) lingual branches for the mucosa of the posterior third of the tongue.

The **vagus nerve** is the longest cranial nerve (Fig. 6.45). It leaves the skull through the jugular foramen, where it emanates a **meningeal branch** for a small part of the meninges in the posterior cranial fossa and the auricular branch of Arnold for the sensory innervation of part of the external acoustic meatus. Directly below the jugular foramen, the vagus nerve features two ganglia, the smaller somatosensory **superior** or **jugular ganglion** and the larger viscerosensory **inferior** or **nodose ganglion**. In the parapharyngeal space, it supplies the soft palate and the pharynx via the pharyngeal branch to the pharyngeal plexus, the larynx via the superior laryngeal nerve and the recurrent laryngeal nerve and the heart via the superior and inferior cervical cardiac branches. The heart is sup-

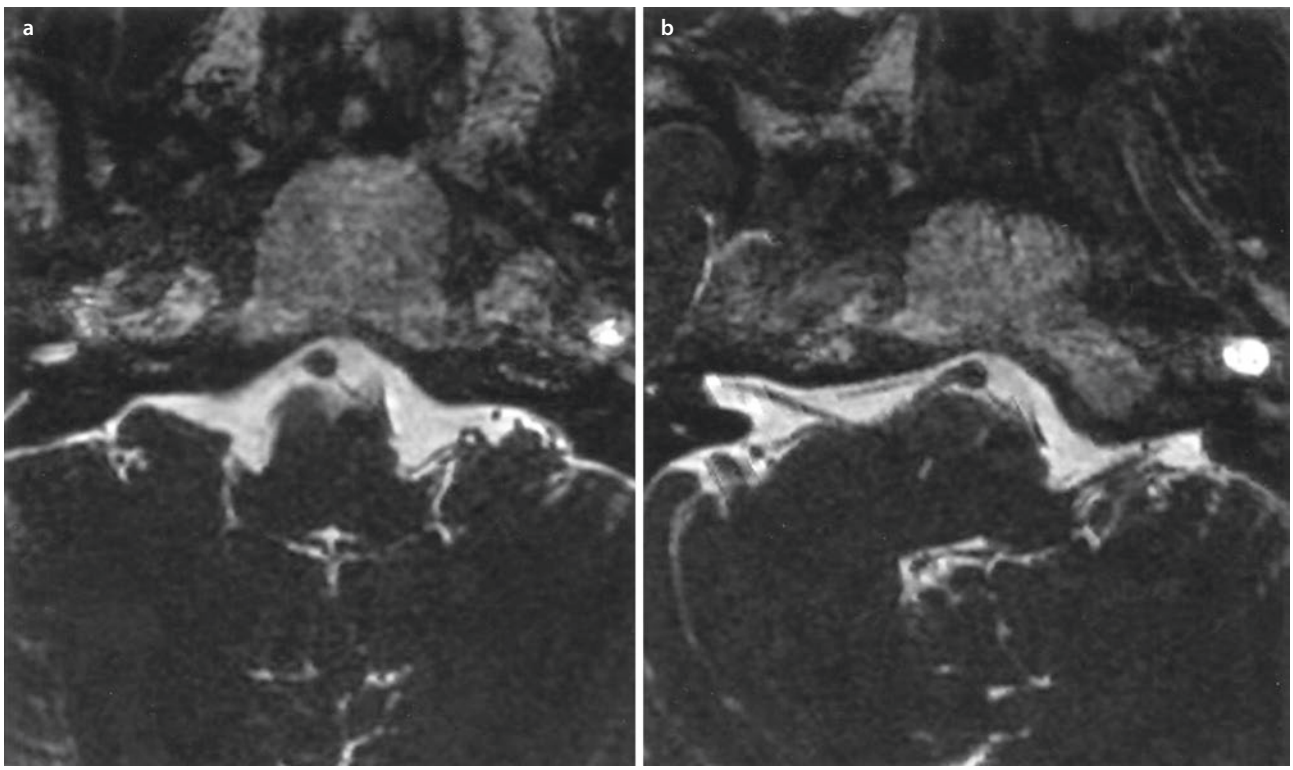

Fig. 6.44 MRIs of the entrance of the glossopharyngeal **a** and vagus nerves **b**

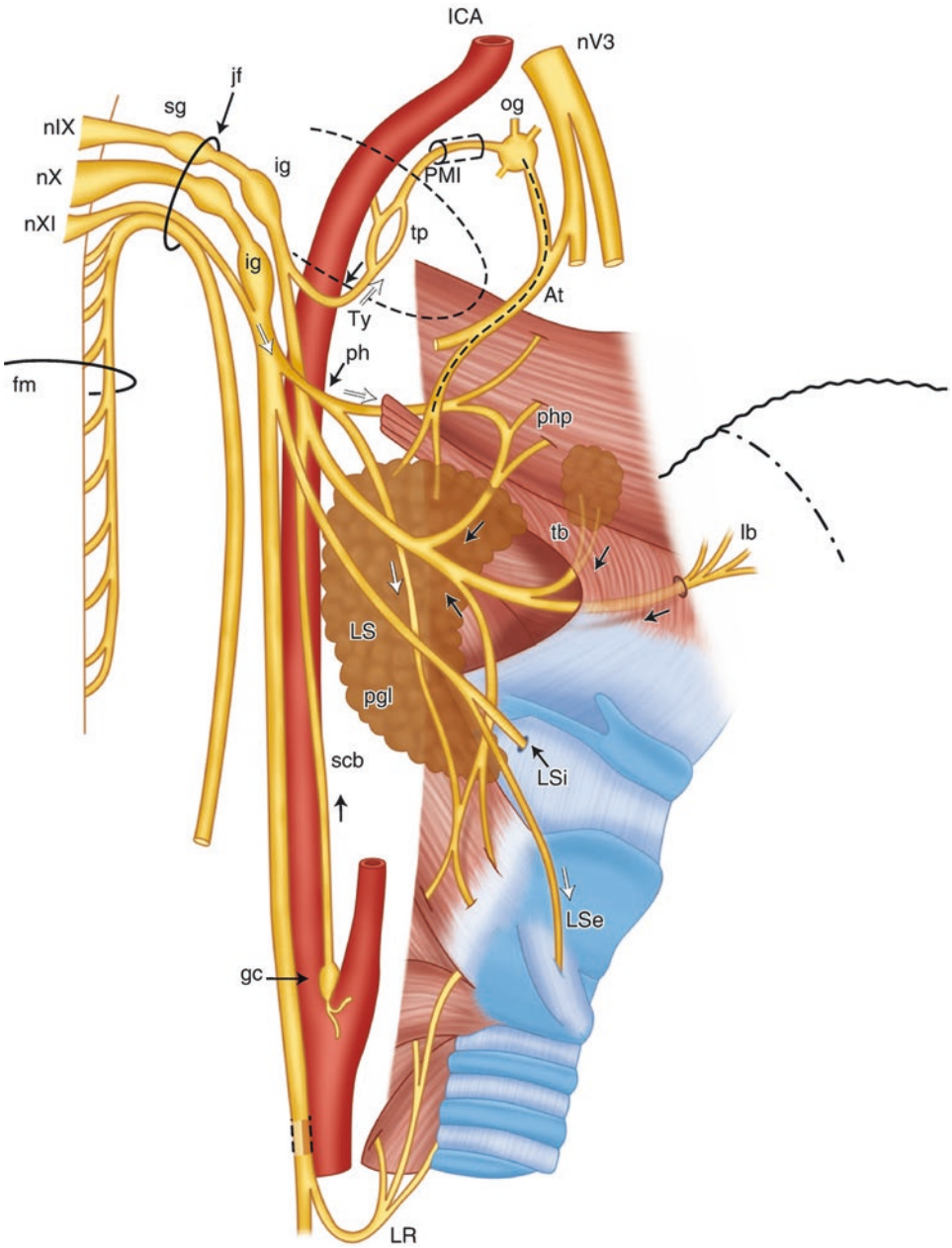

Fig. 6.45 Peripheral course of the glossopharyngeal, vagus and accessory nerves. *At* auriculotemporal nerve, fm foramen magnum, gc glomus caroticum, ICA internal carotid artery, if inferior ganglion, jf jugular foramen, lb lingual branch, LR recurrent laryngeal nerve, LS, LSe, LSi superior laryngeal nerve with external and internal branches, nV3 mandibular nerve, nIX, nX, nXI glossopharyngeal, vagus and accessory nerves, og otic ganglion, pgl parotid gland, ph pharyngeal branches, php pharyngeal plexus, PMI lesser (minor) petrosal nerve, scb carotid sinus branch, sg superior ganglion, tb tonsillar branch, tp tympanic plexus, Ty tympanic nerve. (After ten Donkelaar et al. 2007b; from ten Donkelaar et al. 2018)

plied also via the thoracic cardiac branches, which are sent within the superior mediastinum as well as the bronchial branches and the oesophageal branches to the bronchi and oesophagus, respectively. Finally, it contributes to all visceral plexuses in the abdominal cavity via the vagal trunks (see ► Chap. 12). The glossopharyngeal and vagus nerves participate in many important reflexes such as respiratory and cardiovascular reflexes (see ► Chap. 12) and in swallowing, vomiting and coughing.

Damage to the glossopharyngeal nerve may occur in glossopharyngeal neuralgia or as a result of processes at the jugular foramen. ***Glossopharyngeal neuralgia*** consists of paroxysms of excruciating pain of short duration that are localized in the ear or the throat. The pain's severity resembles that of a trigeminal neuralgia, but the location is different. Neurovascular compression of the nerve within the subarachnoid space may be present. Processes in the vicinity or within the jugular foramen may impair the functions of the glossopharyngeal, vagus and accessory nerves (see ► Clinical Case 6.14). The clinical features of a ***jugular foramen syndrome*** consist of difficulty swallowing as the palatal muscles may be paretic at one side. In addition, the paresis of the sternocleidomastoid and trapezius muscles may result in a torticollis position of the cervical spine directed towards the side of the lesion, because of an imbalance between the right and left muscles. Hoarseness may result from the unilateral loss of function of the laryngeal recurrent nerve of the vagus, interfering with a proper phonation.

Clinical Case 6.14 Lesions of the IXth, Xth and XIth Cranial Nerves

The IXth, Xth and XIth nerves leave the cranial cavity via the jugular foramen together with the sigmoid sinus. Rather closely related to the foramen jugulare is the hypoglossal canal through which the hypoglossal nerve leaves. Another topographically related structure is the sympathetic internal carotid plexus, which ascends to the skull on the internal carotid artery (see ▶ Chap. 12). This means that when the cervical sympathetic is involved in a jugular foramen syndrome, the lesion is certain to be *outside* the skull. Due to the proximity of the last four cranial nerves, several combinations of nerve lesions are possible, depending on the site of the damage. Symptoms include loss of strength or hoarseness of the voice, nasal speech, difficulty in swallowing with nasal regurgitation of fluids or aspiration of food particles with attacks of choking. Patten (1977) distinguished the following syndromes:

1. The ***Vernet syndrome*** of the jugular foramen with damage to the IXth, Xth and XIth nerves. A lesion inside the skull is more likely to cause this restricted syndrome because a lesion outside the skull most likely affects the XIIth nerve and the sympathetic internal carotid plexus as well.
2. The ***Collet-Sicard syndrome*** affecting the last four cranial nerves.

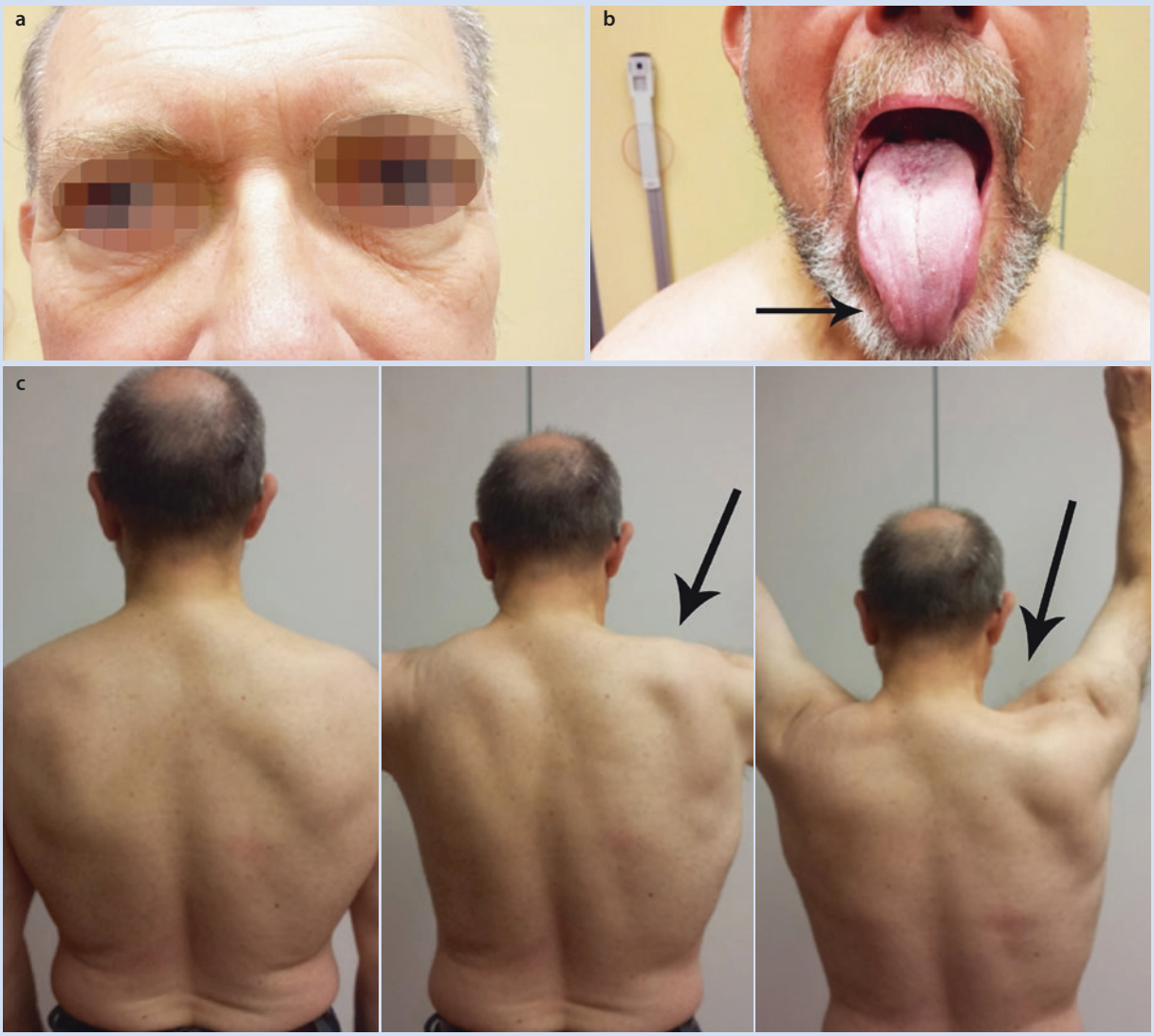

Fig. 6.46 Clinical findings in a patient with a dissection of the internal carotid artery. **a** Slight anisocoria, suggesting Horner syndrome; **b** atrophy of the right part of the tongue, suggesting involvement of hypoglossal nerve; **c** scapula alata and atrophy of trapezius muscle (*arrows*), caused by damage to the accessory nerve. (From Maes and van Domburg 2015; with permission; courtesy Peter van Domburg, Sittard-Geleen)

3. The ***Villaret syndrome*** of the posterior retropharyngeal space, lying immediately behind the nasopharynx, with damage to the last four cranial nerves as well as the cervical sympathetic, resulting in a ***Horner syndrome*** (see **Case report**).

Case report: A 62-years-old right-handed man presented with progressive hoarseness, dysphagia, dysarthria, dyspnoea and pain in his right shoulder, developed over a period of a week. Two weeks earlier, he had experienced a right-sided intense headache. The clinical findings included (Fig. 6.46) a slight anisocoria with a difference in pupil diameter of 2 mm, slight right-sided atrophy of the tongue, hoarseness with absent elevation of the right palatopharyngeal arch. After 2 weeks, a winged scapula (scapula alata) and some weakness at elevation of the right shoulder were noted. Imaging findings included a subtle swelling of the wall of the right internal carotid artery at the level of the craniocervical junction (Fig. 6.47a), suggesting a dissection of the internal carotid artery. This was clearly demonstrated in MRI (Fig. 6.47b, c). The diagnosis was spontaneous dissection of the internal carotid artery leading to the syndrome of Villaret, including ipsilateral paralysis of the cranial nerves IX, X, XI and XII with a partial Horner syndrome due to the involvement of the sympathetic internal carotid plexus surrounding the internal carotid artery.

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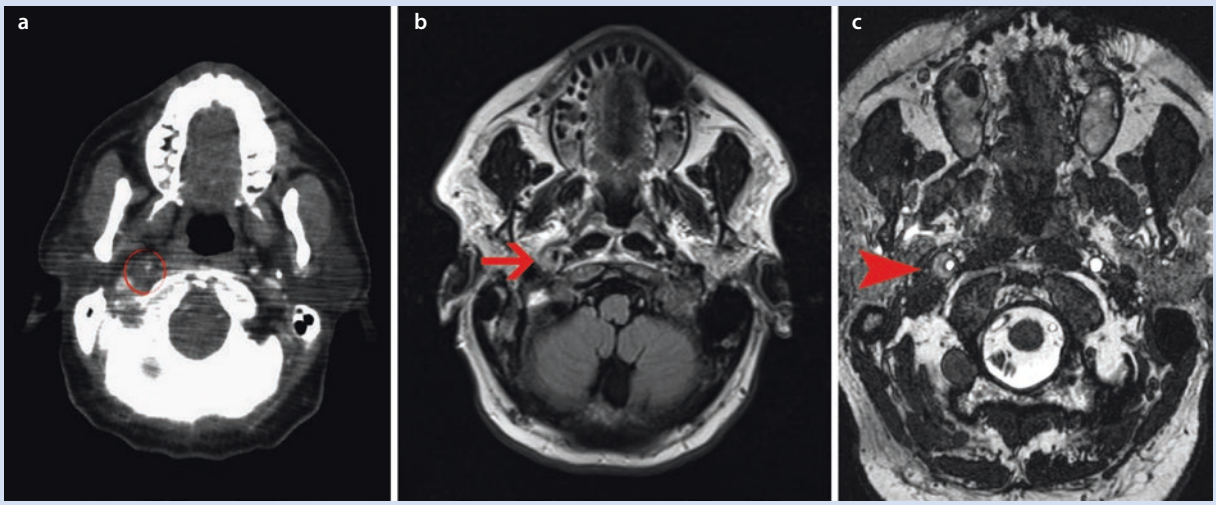
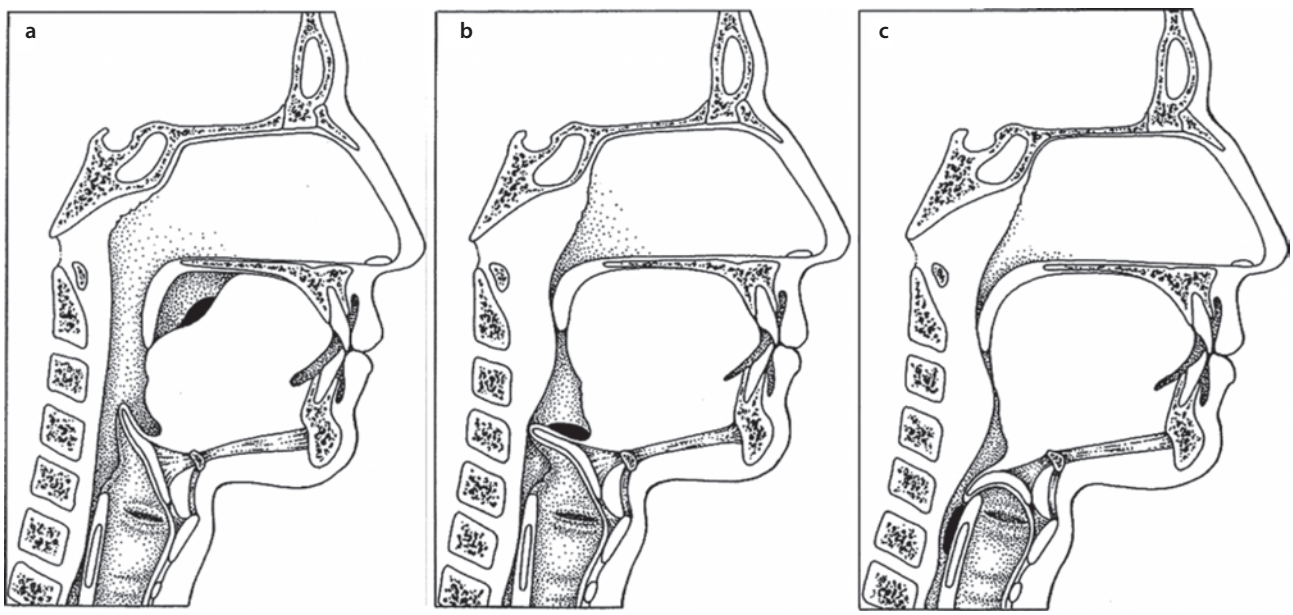


Fig. 6.47 **a** Axial CT showing swelling of the wall of the right internal carotid artery at the level of the foramen magnum; **b** axial T1-weighted MRI showing a narrowed eccentric flow void signal, surrounded by a high-intensity signal of the intramural hematoma in the right internal carotid artery (*red arrow*); **c** axial T2-gradient-echo CISS (constructive interference in steady state) MRI emphasizing the dissection (*red arrow*; from Maes and van Domburg 2015; with permission; courtesy Peter van Domburg, Sittard-Geleen)

6.9.2 Swallowing

Swallowing includes an invariable sequence of muscle activity (Doty 1968; Hockman et al. 1979; Miller 1982). In cats, muscles of the soft palate, tongue, pharynx, oesophagus and larynx and some supra- and infrahyoid muscles participate in swallowing. Different stages of swallowing can be distinguished (◘ Fig. 6.48). The first, buccopharyngeal, stage is characterized by an abrupt onset of activity of the soft palate, upper pharynx, posterior tongue, the mylohyoid and geniohyoid muscles. Lower pharyngeal, oesophageal and laryngeal muscles become active in later stages of swallowing. Many of the motoneurons innervating muscles involved in swallowing are located in the trigeminal and hypoglossal motor nuclei and in the ambiguus nucleus (Mizuno et al. 1975; Uemura et al. 1979; Kalia and Mesulam 1980; Miyazaki et al. 1981; Holstege et al. 1983). In cats, Holstege et al. (1983) showed that motoneurons innervating the soft palate and pharynx are located in the dorsal group of the ambiguus nucleus, whereas motoneurons innervating the upper oesophagus and cricothyroid are located in the retrofacial nucleus, i.e. the most rostral part of the ambiguus nucleus. The caudal pontine tegmentum possibly contains a **swallowing centre** that projects contralaterally to the ventral part of the trigeminal motor nucleus, the dorsal group of the ambiguus nucleus and the ventral part of the hypoglossal nucleus (Holstege et al. 1983). In these areas, motoneurons are located innervating the mylohyoid, soft palate, pharynx and geniohyoid muscles, respectively. Several **pattern generators** for swallowing may be present in the brain stem (Jean 2001; Prosiegel et al. 2005): a dorsomedial medullary generator near the nucleus of the solitary tract, a ventromedial one near the ambiguus nucleus, a pontomedullary centre near the facial motor nucleus and a pontine centre near the trigeminal motor nucleus. In a PET study, Zald and Pardo (1999) found that during voluntary swallowing, the inferior precentral gyrus bilaterally, the right anterior insula and the left cerebellum were activated. The most frequent lesions resulting in ***dysphagia*** are found in the rostral medulla oblongata (Kwon et al. 2005; see ▶ Clinical Case 6.15).



◘ **Fig. 6.48** Stages of swallowing **a–c** with the bolus in *black*. (After ten Donkelaar et al. 2007b)

Clinical Case 6.15 Dysphagia

Case report: A 75-year-old woman was admitted to the intensive care unit because of respiratory insufficiency, leading to clouding of consciousness. For 2 years she had complained of dyspnoe d'effort and dysphagia, but the consulted pulmonologist and cardiologist could not find a cause, apart from a temporary pneumonia. She used a rollator but never complained of weakness or any other focal neurological signs. At admission, there appeared to be hypoventilation without obstructive pulmonary signs and a normal chest X-ray. No signs of pulmonary embolism were present. The unexpected cause of her respiratory insufficiency was demonstrated by MRI when an Arnold-Chiari Type 1 malformation with compression of the medulla oblongata was shown (Fig. 6.49). During admission there was progressive respiratory failure. Neurosurgical decompression was complicated by a postoperative haemorrhage from which she died.

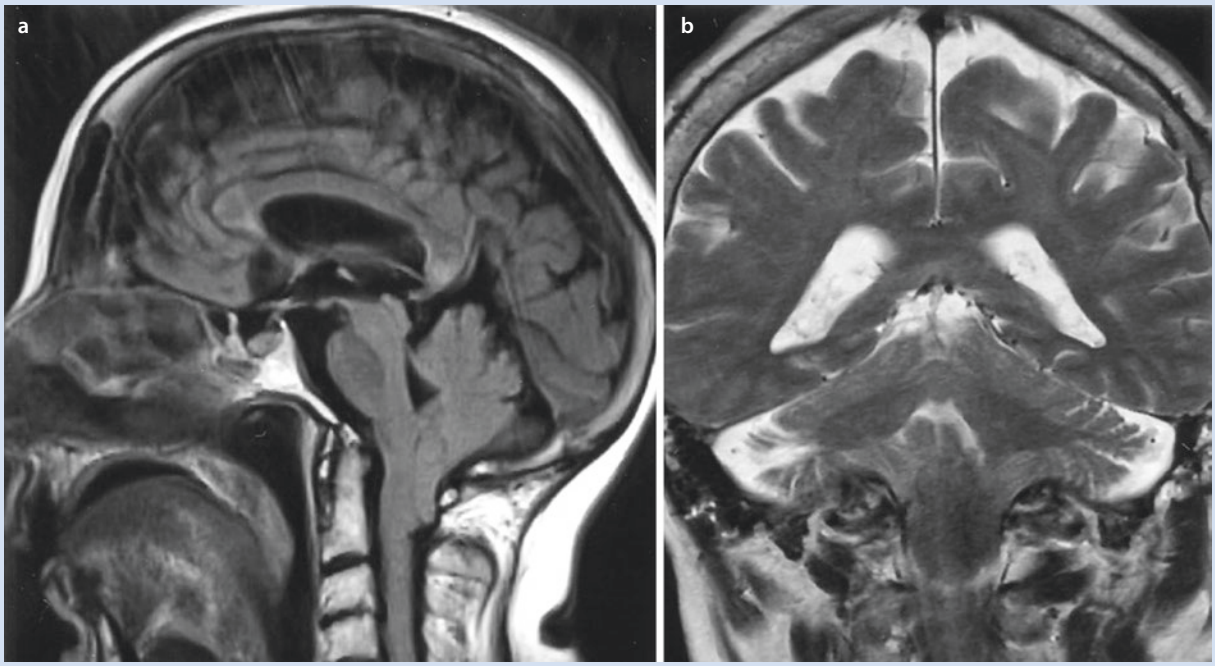


Fig. 6.49 Sagittal T1-weighted **a** and coronal T2-weighted **b** MRIs of an ***Arnold-Chiari Type 1*** malformation with compression of the medulla oblongata resulting in dysphagia. (Courtesy Peter van Domburg, Sittard-Geleen)

6.10 The Hypoglossal Nerve

The axons of the **hypoglossal nerve** leave the medulla oblongata as 10 to 15 slender rootlets between the pyramids and the inferior olive (Fig. 6.50). Its peripheral trajectory is illustrated in Fig. 6.51. The hypoglossal nerve innervates not only the intrinsic tongue muscles but also the extrinsic tongue muscles (the styloglossus, hyoglossus and genioglossus muscles), except for the palatoglossus muscle. It leaves the skull via the hypoglossal canal and gives off the following branches: (1) lingual branches, (2) the geniohyoid branch to the geniohyoid muscle and (3) the thyrohyoid branch to the thyrohyoid muscle. The geniohyoid and thyrohyoid branches do not arise in the hypoglossal nucleus but in the first cervical segments, and they join the hypoglossal nerve. The superior root of the ansa cervicalis from the first cervical nerve joins the hypoglossal nerve below the

skull and leaves it again to innervate the sternohyoid and sternothyroid muscles and the superior belly of the omohyoid muscle.

The **hypoglossal nucleus** consists of several cell groups, each of which innervates a particular tongue muscle (Uemura et al. 1979; Fay and Norgren 1997c). In humans, the hypoglossal nucleus is directly innervated by the corticobulbar tract (Kuypers 1958b). Most of the corticobulbar fibres to the hypoglossal nucleus are crossed, since cortical lesions or lesions of the internal capsule give rise only to contralateral changes in the tongue. Moreover, the hypoglossal nucleus is innervated by the reticular formation (Holstege and Kuypers 1977; Holstege et al. 1977). In rats, Fay and Norgren (1997c) studied the premotor systems controlling the tongue muscles with the transneuronal tracer pseudorabies virus. They found a complex network of multisynaptic connections in the brain stem, remarkably similar to that for the masticatory and facial muscles (see also Ugolini 1995). A lesion of the corticohypoglossal projection results in a ***dysarthrophonia*** (Urban et al. 2001b).

The hypoglossal nerve may be damaged during carotid endartectomy. A ***hypoglossus nerve lesion*** will result in unilateral tongue atrophy. If an attempt is made to protrude the tongue, the tip of the tongue will point towards the paretic side as only the contraction of the contralateral genioglossus will produce protraction of the tongue (see ▶ Clinical Case 6.16). A hypoglossus paresis will contribute to dysphagia since the transport of the food to the pharynx and thereby the initiation of the swallowing reflex is impaired. The pronunciation of the speech is also disturbed. The type of dysarthria resulting from a hypoglossus paresis is often indicated as slurred speech as the lingual consonants cannot be produced properly and has to be differentiated from a bulbar dysarthria.

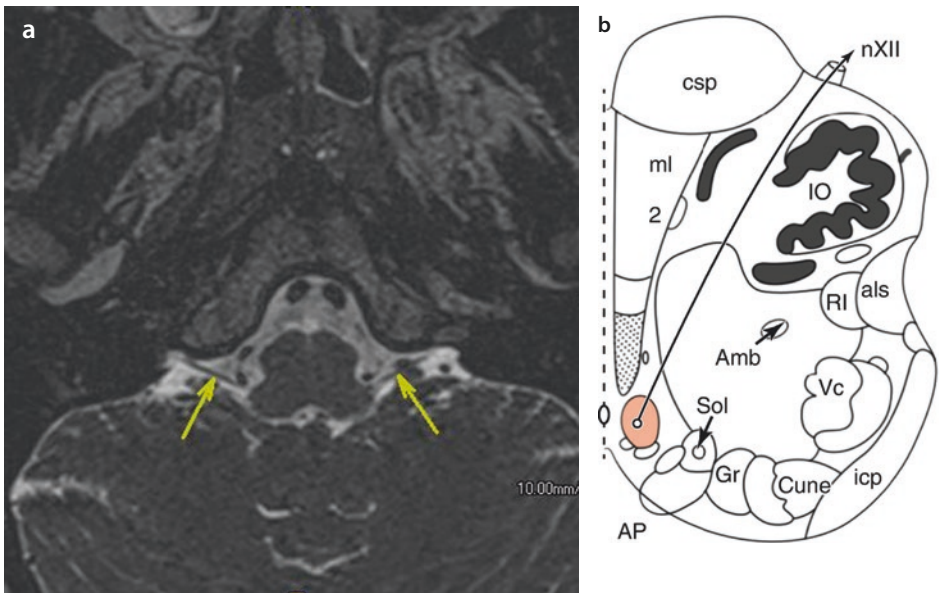


Fig. 6.50 **a** MRI and **b** corresponding horizontal section. (After Duvernoy 1995), showing the exit of the hypoglossal nerve

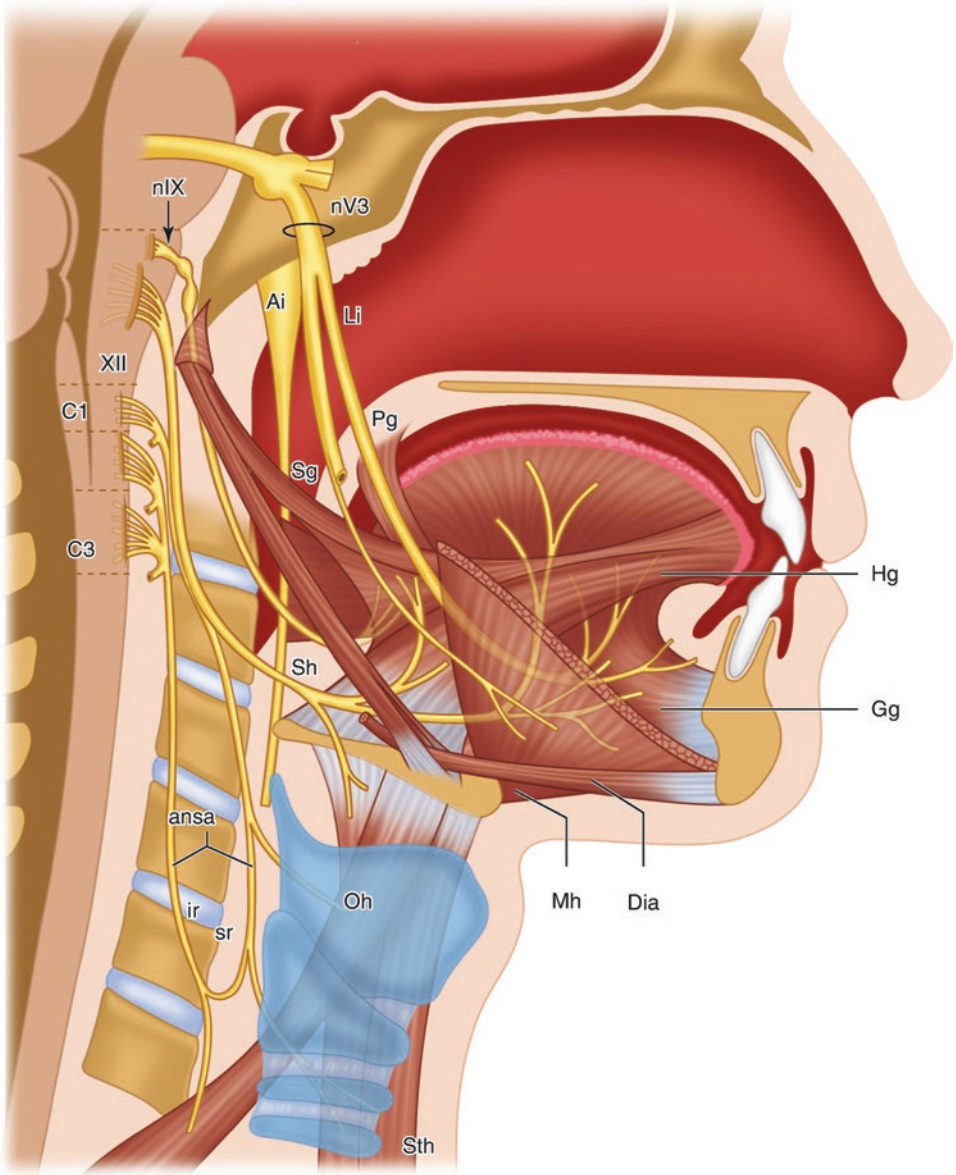


Fig. 6.51 The innervation of the tongue. The hypoglossal nerve and its branches are shown in *black*. Ai inferior alveolar nerve, C1, C3 cervical spinal segments, Dia anterior belly of digastric muscle, Gg genioglossus muscle, Hg hyoglossus muscle, ir inferior root of ansa cervicalis, Li lingual nerve, Mh mylohyoid muscle, nV3 mandibular nerve, nIX glossopharyngeal nerve, Oh omohyoid muscle (superior belly), Pg palatoglossus muscle, Sg styloglossus muscle, Sh stylohyoid muscle, sr superior root of ansa cervicalis, Sth sternohyoid muscle, XII hypoglossal nucleus. (After ten Donkelaar et al. 2007b; from ten Donkelaar et al. 2018)

Clinical Case 6.16 Hypoglossal Paresis

Case report: An 8-year-old girl was seen at the outpatient clinic for progressive clumsiness of her left hand. Neurological examination revealed pyramidal signs in the left arm and leg and atrophy of the tongue. The wasted left side of the tongue and the deviation to the affected side on attempted protrusion (Fig. 6.52) were suggestive of a left lower motoneuron lesion. On MRI, a syringomyelia was diagnosed.

This case was kindly provided by Willy Renier (currently Kortrijk, Belgium).

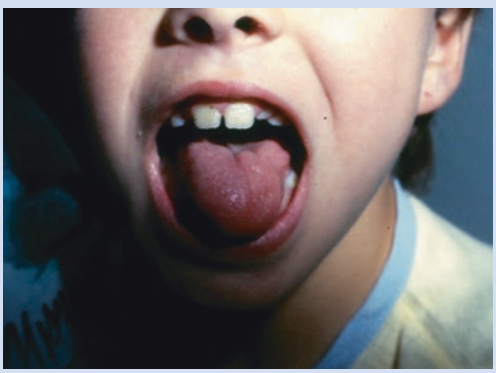


Fig. 6.52 Atrophy of the tongue in an 8-year-old girl. (Courtesy Willy Renier, Kortrijk)

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