Brain Neuroanatomy

3

Adam G. Thomas

Abstract

Unlike certain brain functions, the perception of pain involves multiple different areas of the brain, often working together in functional networks. As such, in order to understand how research, clinical conditions and treatments are related to brain structure and location, an overview of whole brain anatomy is essential. This chapter will commence with a summary of anatomical terms used in relation to the brain and in particular brain imaging. The basic anatomical organisation of different brain compartments will be described, followed by a description of the primary sensory pathways involved in pain perception. A more detailed look at different brainstem areas involved in pain perception and modulation will be followed by an in-depth description of the thalamic nuclei and their cortical connections. Multiple cortical and subcortical areas are involved in both the perception of pain and the response to it. The anatomical localisation of these regions will be described. Finally, the emerging concepts of different functional networks of brain regions relating to attention and emotional aspects of pain processing will be described.

Keywords

Thalamic nuclei · Functional anatomy · Brainstem · Angiography · Tractography · Norepinephric · Raphe magnus · Cortical regions

1 Introduction

Unlike certain brain functions, the perception of pain involves multiple different areas of the brain, often working together in functional networks. As such, in order to understand how research, clinical conditions and treatments are related to brain structure and location, an overview of whole brain anatomy is essential. This chapter will commence with a summary of anatomical terms used in relation to the brain and in particular brain imaging.

A.G. Thomas (✉)
Department of Neuroradiology, Nottingham University Hospitals NHS Trust, Queens Medical Centre Campus, Derby Road, Nottingham NG7 2UH, England
e-mail: adam.thomas@nuh.nhs.uk

L. Saba (ed.), *Neuroimaging of Pain*, DOI 10.1007/978-3-319-48046-6_3

The basic anatomical organisation of different brain compartments will be described, followed by a description of the primary sensory pathways involved in pain perception. A more detailed look at different brainstem areas involved in pain perception and modulation will be followed by an in depth description of the thalamic nuclei and their cortical connections. Multiple cortical and subcortical areas are involved in both the perception of pain and the response to it. The anatomical localisation of these regions will be described. Finally, the emerging concepts of different functional networks of brain regions relating to attention and emotional aspects of pain processing will be described.

2 Neuroanatomical Localisation and Terms

Anatomical figures in this chapter will be based around clinical neuroimaging studies. It is important to be familiar with the conventional way in which clinical studies and anatomical information is described. Most brain studies rely on cross sectional imaging of the brain, presented in 3 different anatomical planes: sagittal, axial and coronal (Fig. 1).

Neuroradiological convention is to present axial images as if viewing the patient from the feet, looking up to the top of the head. As such the patient/subject's right side is presented on the left side of the image. This is also the case when viewing coronal images. It is conventional to present sagittal images with the nose/front of the face to the left of the image and the back of the head at the right (Fig. 2).

As a word of caution however, it should be noted that frequently in psychology literature (particularly in the presentation of functional MRI data) this convention is not followed, with the right side of the patient being to the right of the image and the legends of any published image should be carefully inspected.

The naming of brain structures frequently uses anatomical descriptors such as anterior/posterior,

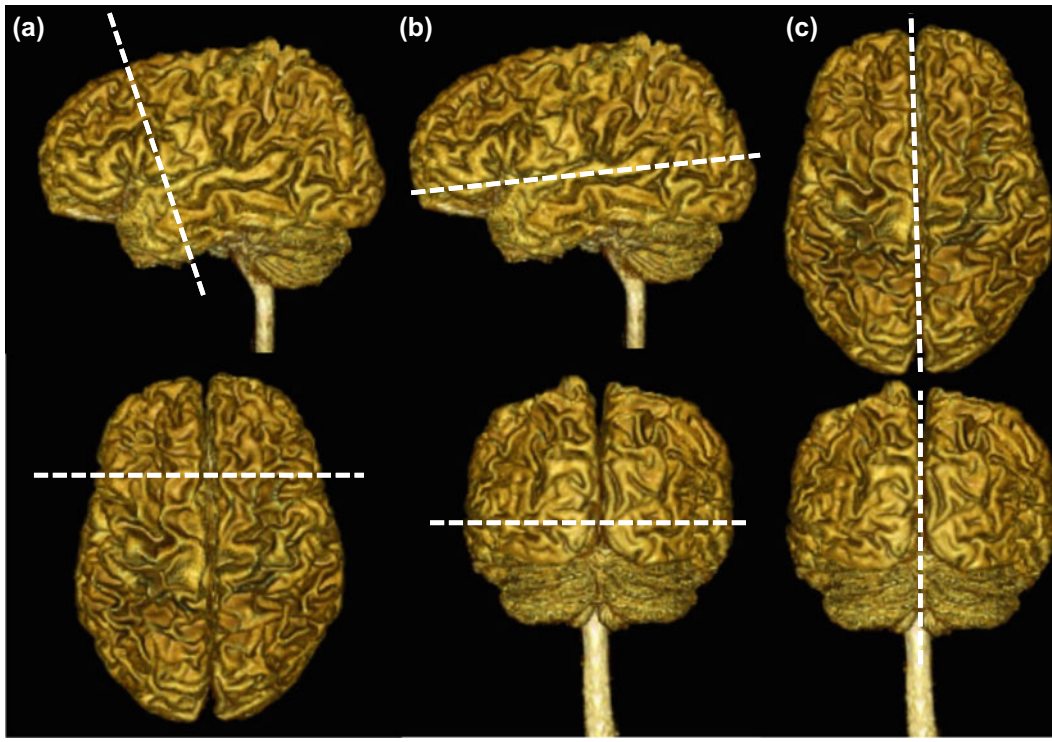

Fig. 1 3d surface shaded display showing the coronal plane (**a** *top row* viewed from side, *bottom row*, viewed from above), axial plane (**b** *top row* viewed from side, *bottom row* viewed from front) and sagittal plane (**c** *top row* viewed from above, *bottom row* viewed from front)

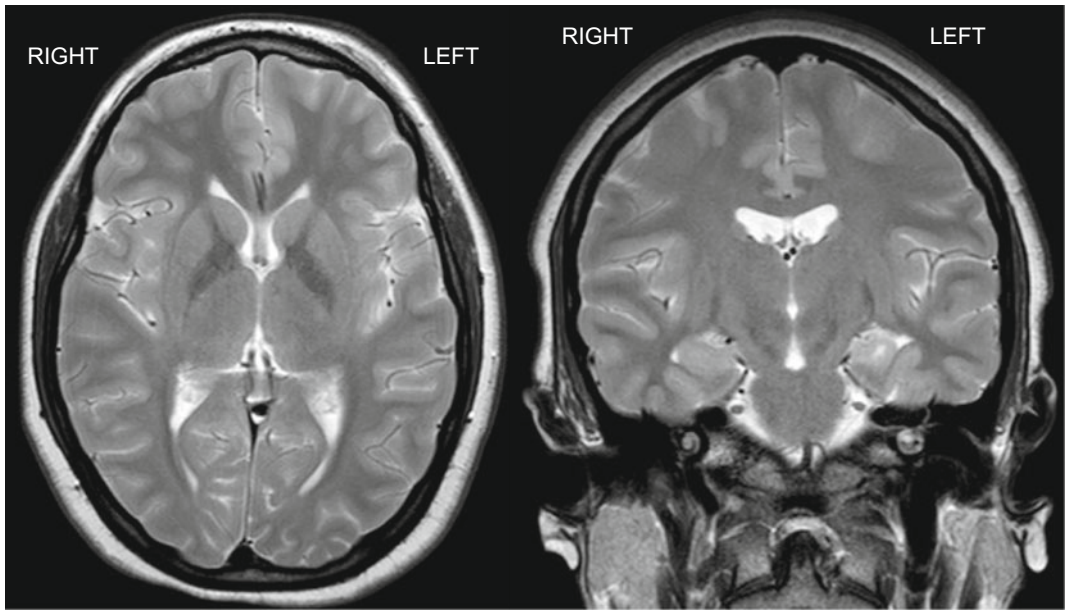

Fig. 2 Axial T2 (*left*) and coronal T2 (*right*) showing conventional radiological anatomical orientation

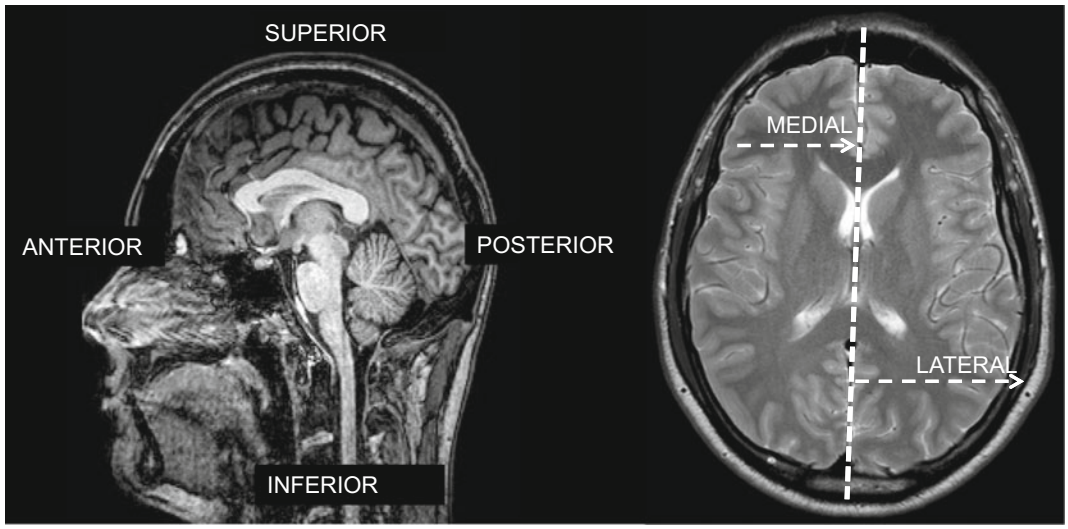

Fig. 3 Anatomical labelling. Sagittal T1 volume (MPRAGE) *top left*, axial T2, *bottom right*. The term 'medial' is used for structures close to the *midline*; lateral is used for structures further away from the *midline*

superior/inferior and right/left. These directions in relation to brain imaging are shown in Fig. 3.

The names of some structures relates to their embryological origin, reflecting the trilaminar disc created during gastrulation, before the complex folding that occurs to form the central nervous system [1]. The term dorsal and ventral are still used when describing anatomical localisation in the spine. The use of the term ventral and dorsal in the brain refers to the basal/inferior

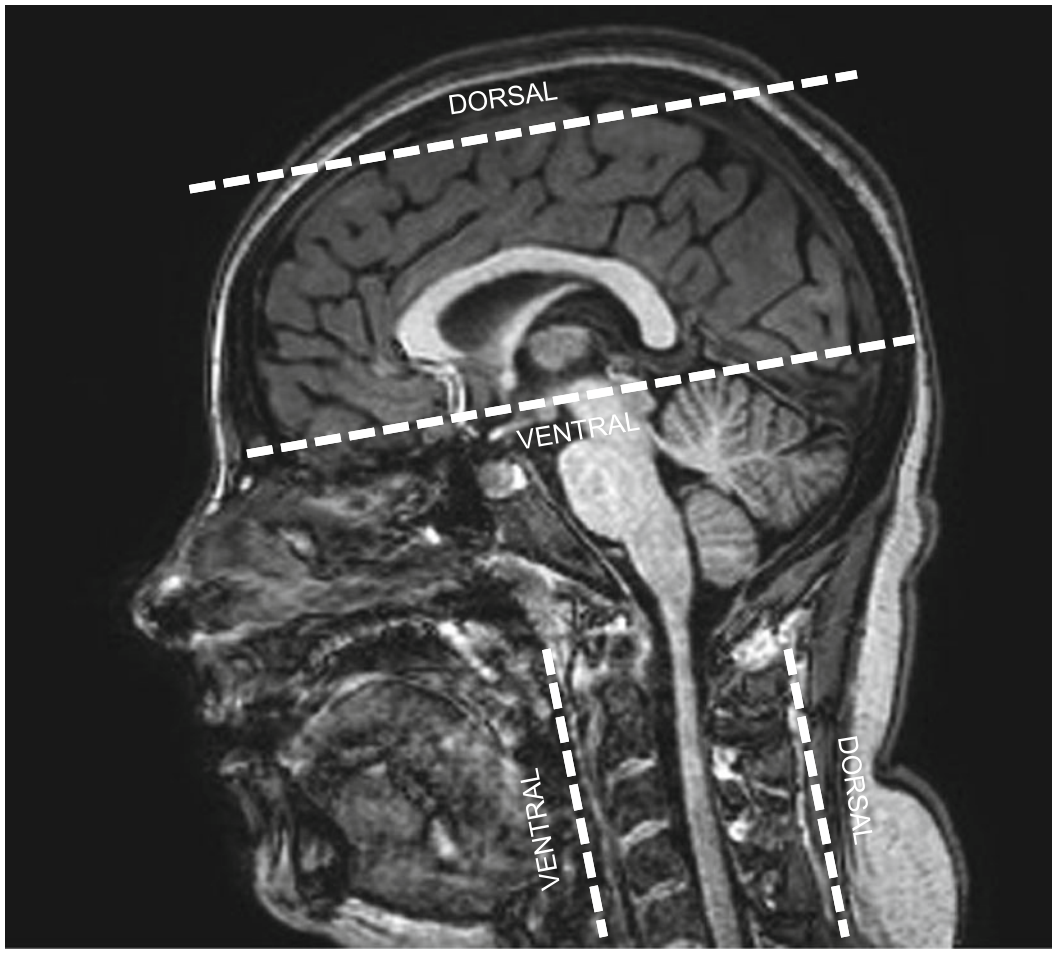

Fig. 4 Sagittal T1 volume showing different orientations of the terms 'dorsal' and 'ventral' in the spine and brain, reflecting folding of the common embryological precursor

surface and superior surfaces respectively whereas in the brainstem it refers to the anterior and posterior surfaces respectively (Fig. 4).

3 Basic Brain Structure

The brain is divided into two main compartments by the tentorium cerebelli, a fibrous dural reflection that separates the posterior fossa, beneath the tentorium, from the cerebrum, lying above it. This division reflects the embryological origin of different structures: all structures above the tentorium develop from the embryological diencephalon and prosencephalon, whereas infratentorial structures derive from the mesencephalon and metencephalon. In the mature brain the posterior fossa contains the brainstem and cerebellum, whereas the supratentorial compartment contains the cerebral cortex, deep grey matter and hypothalamus (Fig. 5) [1].

The mature adult brain is arranged with the heavily folded cortex around the outside or surface with white matter beneath it. There is further grey matter deep within the brain in the form of the basal ganglia, amgydala and thalami. The cerebellum is similarly arranged with the cerebellar cortex arranged around the outside or surface and deep grey matter nuclei situated centrally (Fig. 6) [2].

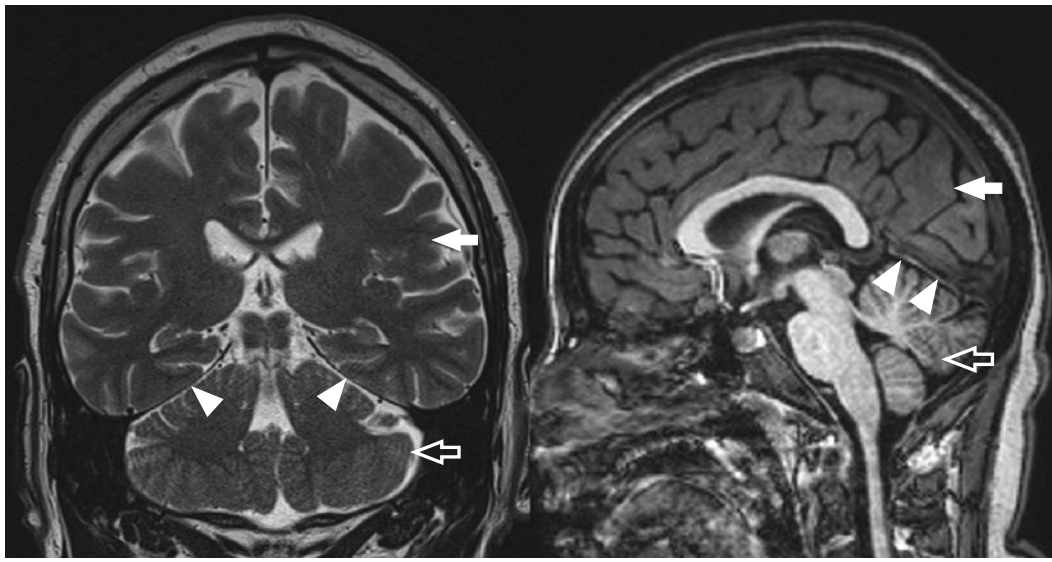

Fig. 5 Coronal T2 image (*left*), sagittal T1 volume (MPRAGE) (*right*). The supratentorial compartment (*solid white arrow*) is located above the tentorium cerebelli (*white arrowheads*); the infratentorial compartment is located beneath the tentorium (*open white arrow*)

The basal ganglia include the globus pallidus, caudate nucleus and putamen. The latter two are sometimes referred to as the corpus striatum, whereas the combination of the globus pallidus and putamen are referred to as the lentiform nucleus. The hockey-stick-shaped white matter between the caudate and lentiform nucleus and thalamus is the internal capsule (Fig. 7) [2].

4 Supratentorial Landmarks

The brain can be divided in lobes with broadly similar functions based on external landmarks formed by various prominent sulci. The frontal lobe is separated from the parietal lobe by the central sulcus, sometimes called the Rolandic fissure. In addition to being responsible for executive functions such as planning, motivation etc., the frontal lobe contains the primary and supplementary motor areas and Broca's area, responsible for speech production in the inferior frontal gyrus. The parietal lobe contains the primary somatosensory cortex, located in the postcentral gyrus but also performs many complex integrative functions including calculation, orientation in space and visual processing (Fig. 8) [3].

The largest 'sulcus' visible on the side of the brain is the Sylvian fissure. This landmark separates the temporal lobe, below, from the frontal and parietal lobes superiorly. The temporal lobe contains the primary auditory cortex and medially the limbic system structures involved in memory formation—primarily the hippocampus and associated gyri. The temporal lobes also contribute to visual processing (particularly visual form—e.g. face recognition) and are also important in understanding of speech—Wernicke's area is located at the junction of the superior temporal lobe and parietal lobe at the back of the Sylvian fissure (Fig. 9).

The occipital lobe is located in a paramedian location posteriorly and contains the primary visual cortex. The junction with the parietal lobe is marked on the medial surface by the parieto-occipital sulcus; the junction with the temporal and parietal lobe on the surface of the brain is less well defined (Fig. 10).

The limbic system is often referred to as a separate lobe of the brain although is made of multiple separate structures. It is one of the oldest

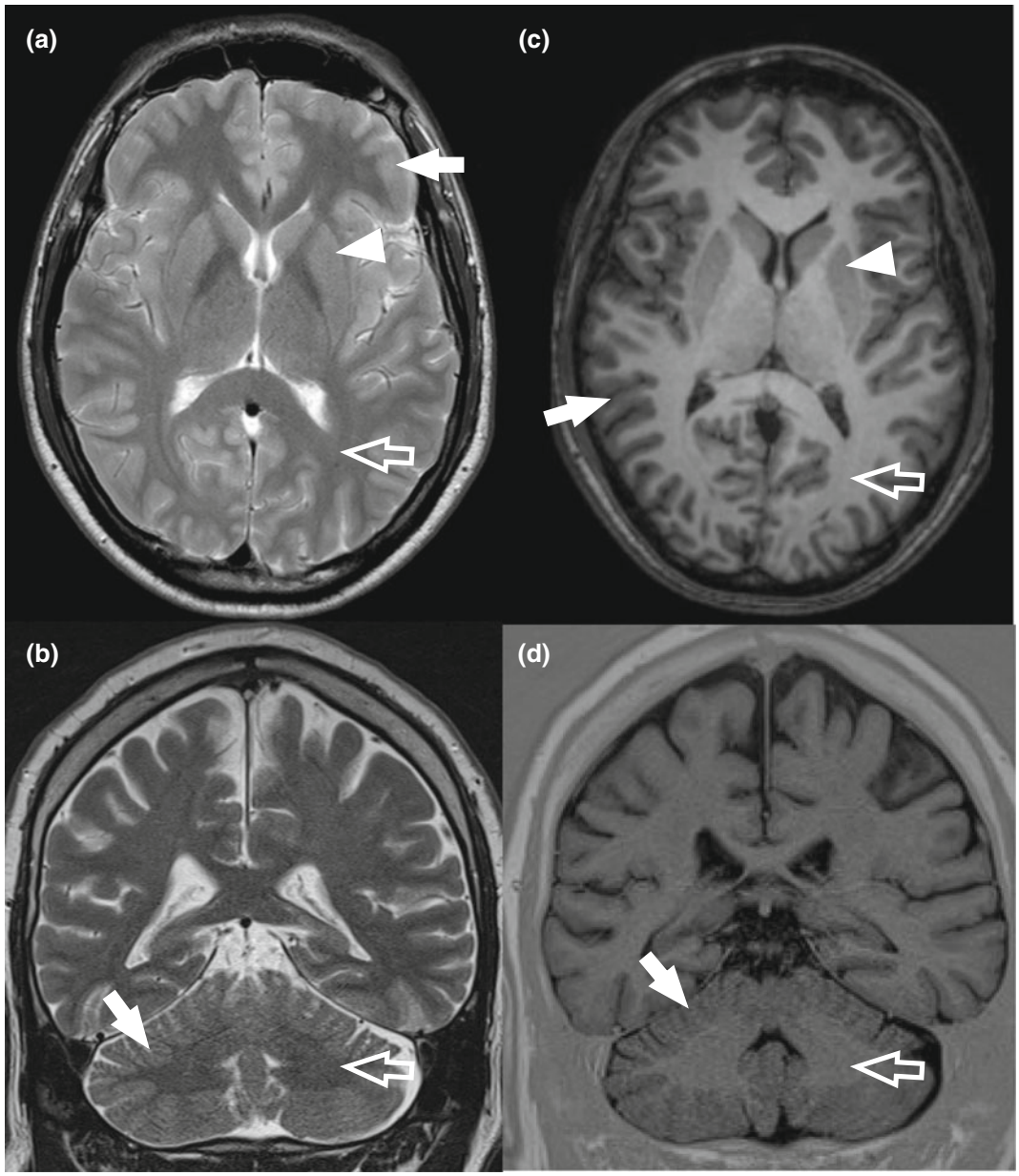

Fig. 6 Axial and coronal T2 (**a**, **b**), axial T1 volume (**c**) and coronal T1 inversion recovery (**d**). The cortical grey matter (*solid white arrows*) is arranged around the periphery of the cerebrum and cerebellum. The deep grey matter of the basal ganglia (*arrowhead*) is located centrally. The white matter (*open white arrows*) is situated beneath the cortical grey matter and surrounds the basal ganglia

parts of the brain (phylogenetically) and contains mesocortex (4 cortical layers as opposed to the 6 found in the neocortex). In addition to the amygdala and hippocampus located in the medial temporal lobe/temporal lobe uncus, the limbic system incorporates the fornix (the hippocampal outflow tract), the cingulate gyrus—the gyrus wrapping around the corpus callosum and also the insular cortex, deep within the Sylvian fissure (Fig. 11) [4]. Many of these structures are part of

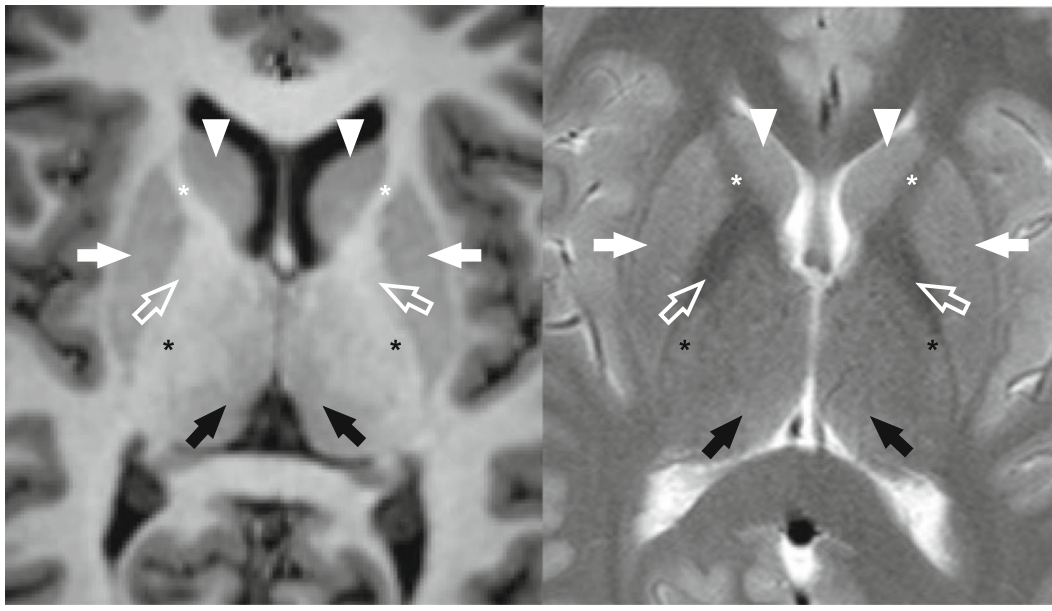

Fig. 7 Axial T1 volume (*left*) and T2 (*right*) showing the heads of the caudate nucleus (*white arrowheads*), the putamen (*white arrows*), the globus pallidus (*open white arrow*, best visualised on T2 due to hypointense mineralisation), the thalami (*black arrows*), the anterior limb of the internal capsule (*white asterisks*) running between the caudate and putamen and the posterior limb of the internal capsule (*black asterisks*) running between the putamen and thalamus

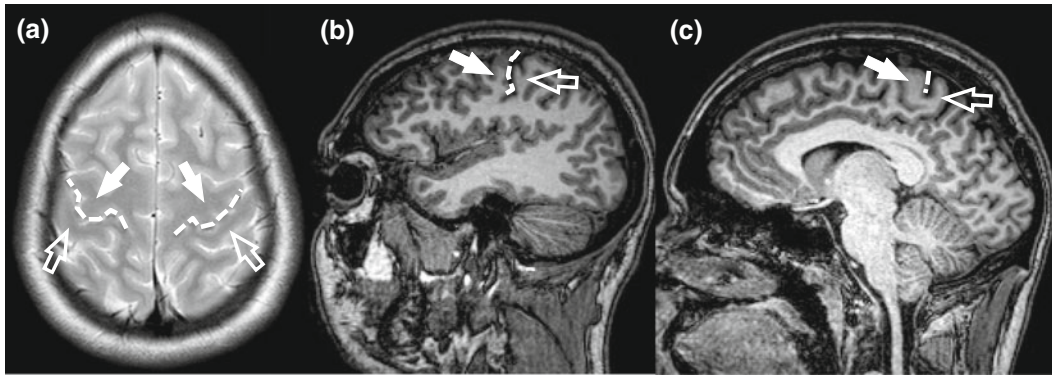

Fig. 8 Axial T2 (**a**), parasagittal MPRAGE T1 volume (**b**, **c**) showing position of the central sulcus (*dashed line*), separating the pre-central gyrus (*solid white arrow*) from postcentral gyrus (*open white arrow*). The frontal lobe is anterior to the central sulcus; the parietal is posterior to the central sulcus. Note how far posteriorly the frontal lobe extends on the sagittal imaging

the Papez circuit involved in the laying down of new memories [5]; the amygdala is also involved in fight-or-flight responses and emotional responses [6].

The fluid filled spaces within the centre of the brain are called the ventricular system and contain cerebrospinal fluid (CSF). The ventricles are continuous with each other via various foraminae: the lateral ventricles and third ventricles in the supratentorial compartment are connected via the foramen of Monro; the third and fourth ventricle are connected via the aqueduct of Sylvius which

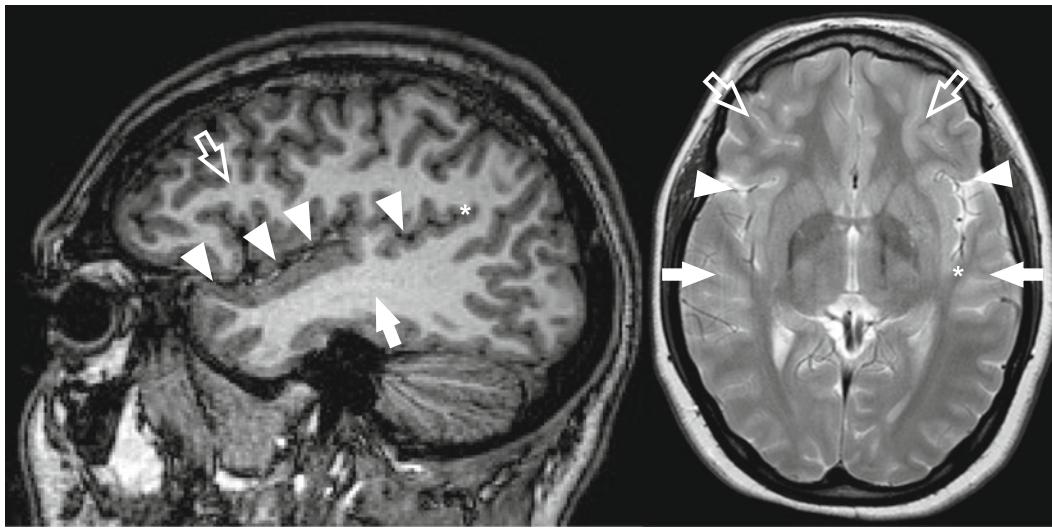

Fig. 9 Para-sagittal T1 volume (*left*) and axial T2 (*right*). The sylvian fissure (*white arrowheads*) separates the temporal lobe (*solid white arrow*) from the frontal lobe anteriorly (*open white arrow*) and parietal lobe posteriorly (*black arrow*). Wernicke's area is shown by the *asterisk*

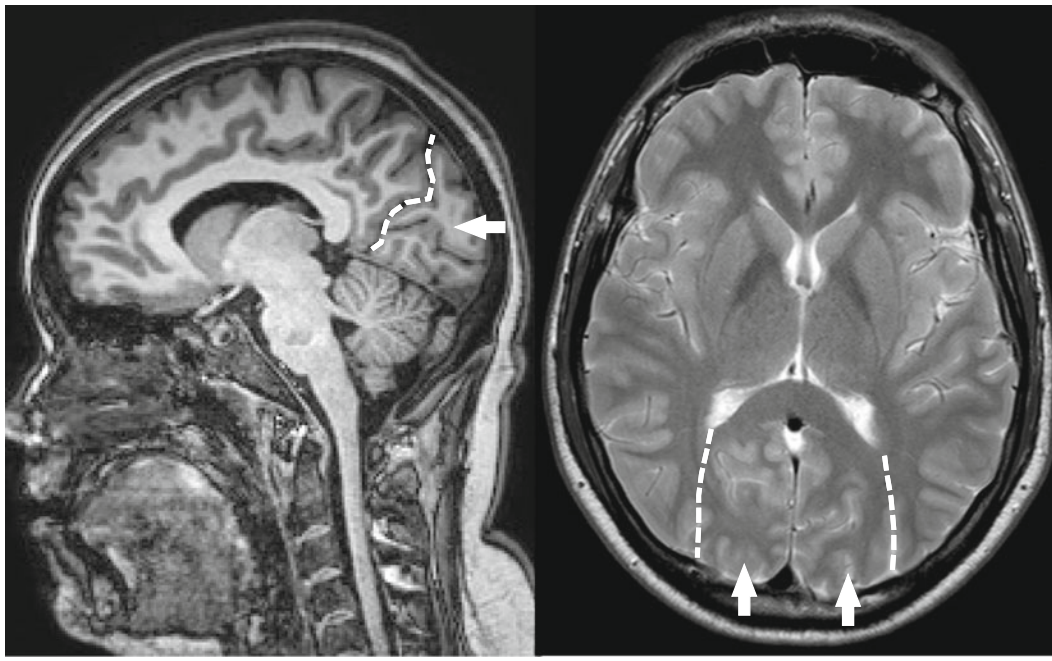

Fig. 10 Parasagittal T1 volume (*left*) and axial T2 (*right*) showing the occipital lobes (*white arrows*). The boundary between the parietal and occipital is clearly visible in the sagittal plane, marked by the parieto-occipital sulcus (*dashed line, left*). The boundary in the axial plane is less well defined and is approximated by the territory of supply of the posterior cerebral artery (approximate location shown by *dashed lines, right*)

runs through the midbrain. The fourth ventricle is connected to the central canal of the spinal cord inferiorly and also the subarachnoid space over the cerebral convexities via two exit foramina: the foramen of Magendie in the midline and foramina of Luschka, laterally (Fig. 12) [2].

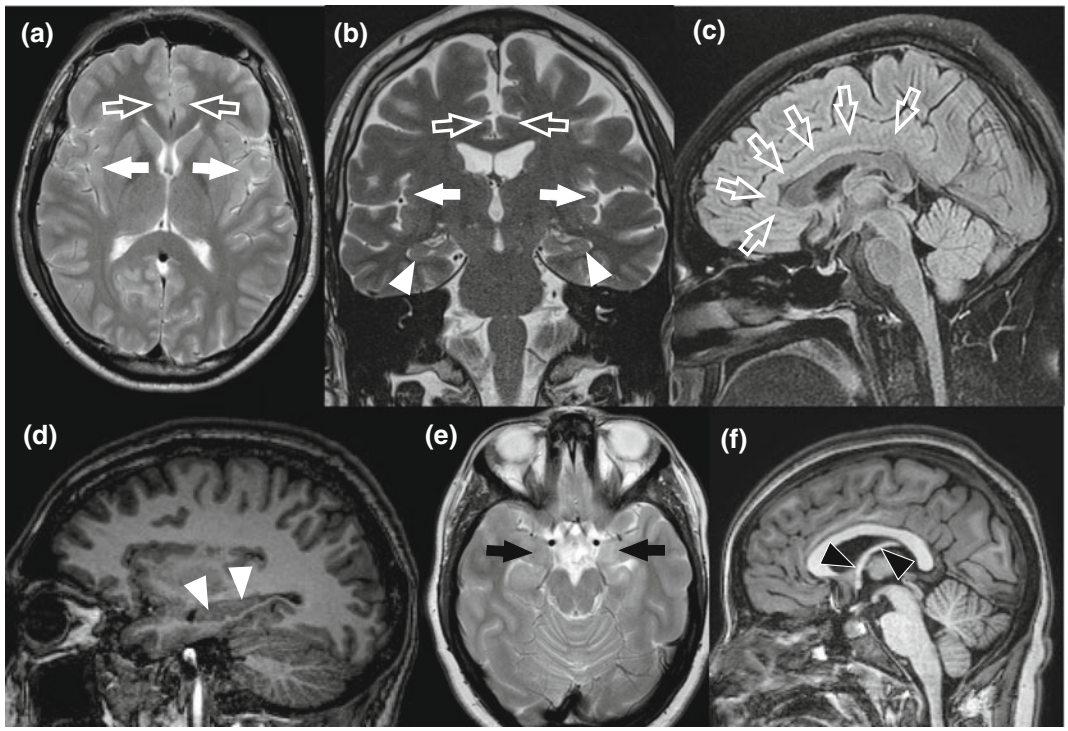

Fig. 11 Limbic system. Axial T2 (**a**, **e**), coronal T2 (**b**), sagittal FLAIR (**c**) and sagittal T1 volume (**d**, **f**). The insular cortex is shown by the *closed white arrows*; the cingulate cortex (*open white arrows*) wraps around the corpus callosum in the midline. The hippocampus is demonstrated in the medial temporal lobes (*white arrowheads*). The amygdala is the small grey matter nucleus in the medial temporal lobe immediately anterior to the hippcampus (*black arrows*). The outflow tract of the hippocampus, the fornix, is shown by the *black arrowheads* (**f**)

White matter

Although it appears fairly homogenous on standard structural imaging (e.g. T1 and T2 weighted MRI) the cerebral white matter is a highly ordered structure containing multiple different fibres and tracts running in different directions. These larger tracts are elegantly displayed by diffusion tensor imaging (DTI) with colour coding representing the main direction of the tracts displayed (directionally encoded colour—DEC) (Fig. 13) [7].

Commissures are tracts that connect the two different hemispheres of the brain, the larges of which is the corpus callosum. Other commissures include the anterior commissure, connecting the temporal lobes; the posterior commissure, at the posterior limit of the third ventricle, the hippocampal commissure (where the two fornices temporarily join) and the habenular commissure in the pineal region (Fig. 14).

Fasciculi are tracts connecting different regions of the brain in the same hemisphere. In the supratentorial brain these include the superior and inferior longitudinal fasciculi—running in an anteroposterior direction; and the uncinate fasciculus, connecting the ipsilateral frontal and temporal lobes via the external capsule (Fig. 15) [7].

Major tracts run in a superoinferior direction connecting the supratentorial brain with the cerebellum, brainstem and spinal cord. The largest of these are the corticospinal tracts—the motor output of the brain to the spinal cord (Fig. 16) [8]. Ascending sensory pathways through the brainstem and supratentorial brain will be considered later.

Although difficult to visualise, even with DTI, it is important to be aware of the functional concept of

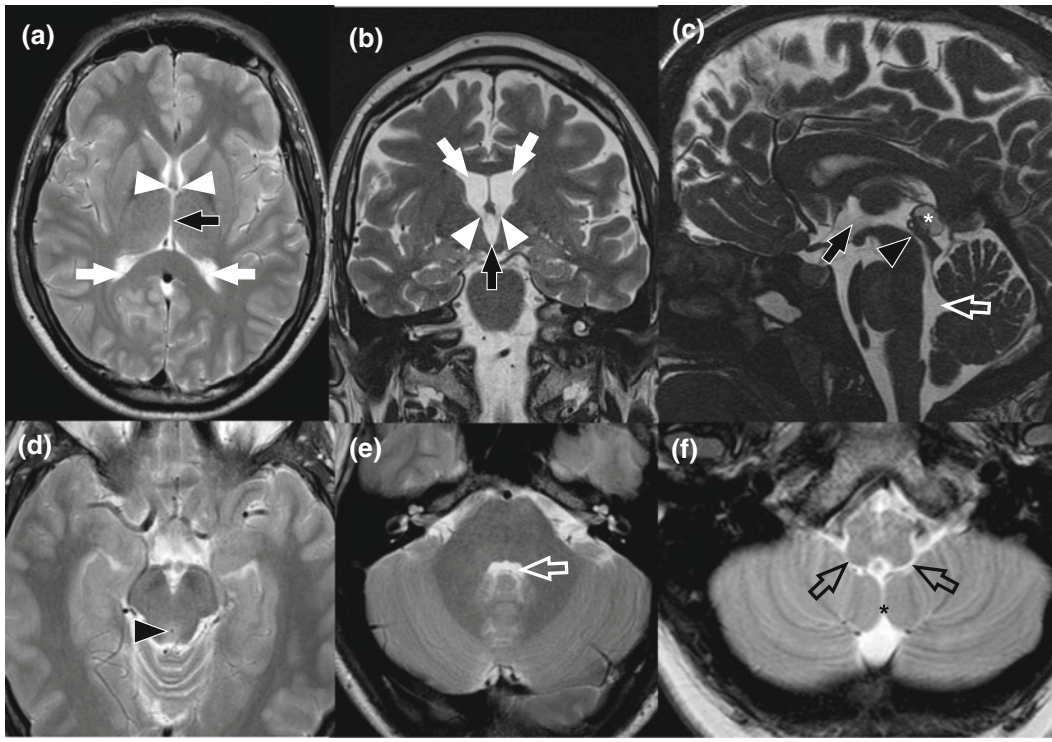

Fig. 12 Axial T2 (**a**, **d**–**f**), coronal T2 (**b**), sagittal 3d T2 (**c**). CSF is produced in the lateral ventricles (*solid white arrows*) and passes through the foramina of Monro (*white arrowheads*) into the third ventricle (*black solid arrow*). From there it passes through the cerebral aqueduct (of Sylvius) (*black arrowheads*) into the fourth ventricle (*white open arrow*). From the fourth ventricle it passes into the subarachnoid space around the surface of the brain and spinal cord via the foramina of Magendie (*black asterisk*) and Luschka (*open black arrows*). Incidental pineal cyst noted (*white asterisk*)

cortical–subcortical loops connecting the cortex and deep grey matter structures. These connections between the thalami and basal ganglia and the cortex are reciprocal and continually supply feedback to cortical areas, also integrating sensory information from the spinal cord in the thalami. For example fibres from the primary motor cortex terminate on the putamen which via either the direct or indirect pathways connect to the internal segment of the globus pallidus (integrating input from the subthalamic nucleus and substantia nigra); the GP interna output travels to the anterior/lateral nuclei of the thalami which in turn project back to the primary motor cortex. This system serves to modulate and fine tune movement [2, 3]. The thalami contain multiple internal nuclei with different reciprocal cortical connections; their functional importance with regard to pain perception will be considered later.

5 Infratentorial Landmarks

The brainstem can be divided into three segments, running cranially to caudally: the midbrain, pons and medulla. The cerebellum is located dorsal to the brainstem spanning the distance from the intercollicular sulcus of the midbrain to the obex (inferior limit) of the fourth ventricle behind the medulla (Figs. 17 and 18) [9].

The midbrain contains the IIIrd and IVth cranial nerve nuclei, the structures of the substantia nigra and red nuclei. The pons contains the reticular activating system and a diffuse network of other pontine nuclei along with the cranial nerve nuclei of the Vth to the VIIth nerves (at the pontomedullary junction). The medulla contains

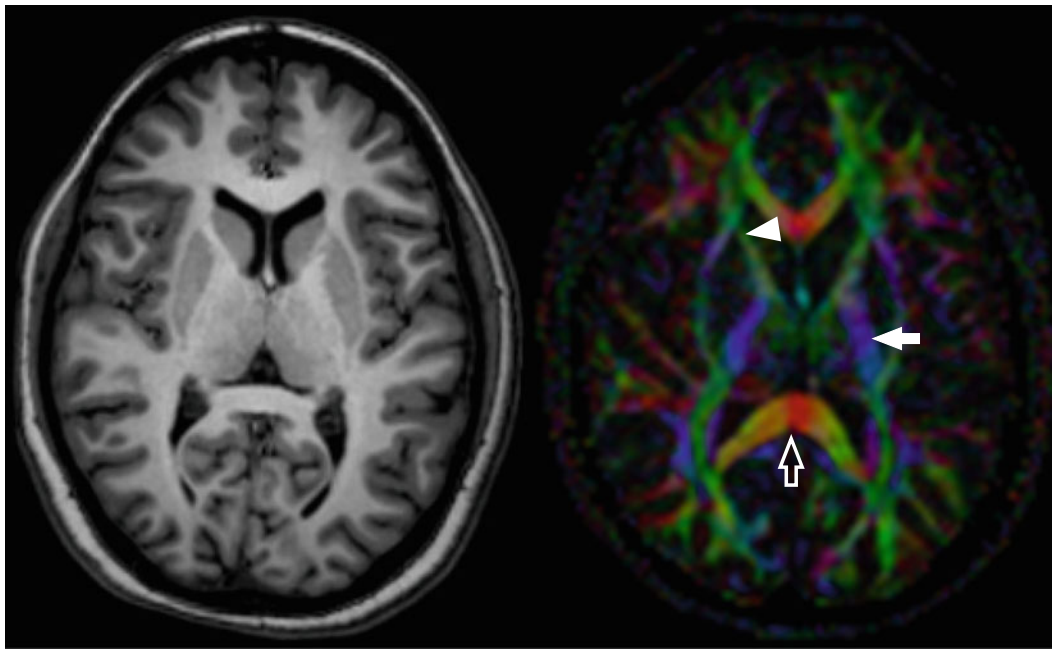

Fig. 13 *Left*, axial T1 volume, *right* DTI directionally encoded colour map. The white matter on the T1 image appears featureless but DTI allows identification of the orientation of fibre tracts: the corticospinal tracts (*white arrow*) are demonstrated in a superoinferior orientation coloured *blue*; the corpus callosum (*open white arrow*) is coloured *red* passing from left to right; the anterior limb of the internal capsule (*arrowhead*) is oriented in the anteroposterior direction and coloured *green*

the remaining VIIIth–XIIth cranial nerve nuclei along with important cardiorespiratory centres.

In addition to the corticospinal tracts running through the brainstem to the spinal cord, other longitudinal tracts can be identified. The medial longitudinal fasciculi connect the cranial nerve nuclei of the IIIrd, IVth and VIth nuclei, and along with the parapontine reticular formation are involved in coordinating eye movements. The sensory tracts running through the brainstem to the thalamus will be described in detail later.

6 Blood Supply of the Brain

The arterial supply to the brain can be split into vessels arising from the carotid, or 'anterior' circulation and those arising from the vertebrobasilar, or 'posterior' circulation. These two systems communicate via a vascular ring situated at the base of the brain called the circle of Willis. The major blood vessels supplying the supratentorial brain are the anterior, middle and posterior cerebral arteries. The largest branch is the middle cerebral artery (MCA) which supplies the majority of the frontal, temporal and parietal lobes along with the basal ganglia. The anterior cerebral arteries (ACAs) supply the medial part of the cerebral hemispheres anteriorly. The posterior cerebral arteries (PCAs) supply the medial surface of the brain posteriorly (the occipital lobes) and also the posterior aspect of the thalami (Fig. 19) [10].

The posterior fossa structures are supplied either directly, or via branches of the vertebral and basilar arteries. The three largest cerebellar arteries are the posterior–inferior cerebellar artery (PICA), the anterior–inferior cerebellar artery (AICA) and superior cerebellar artery (SCA). Much of the brainstem is supplied by small, perforating branches of the basilar artery directly (Fig. 20).

The venous drainage system is made up of the deep cerebral veins and dural venous sinuses. Superficial cortical veins also drain into the dural venous sinuses, which eventually join together at

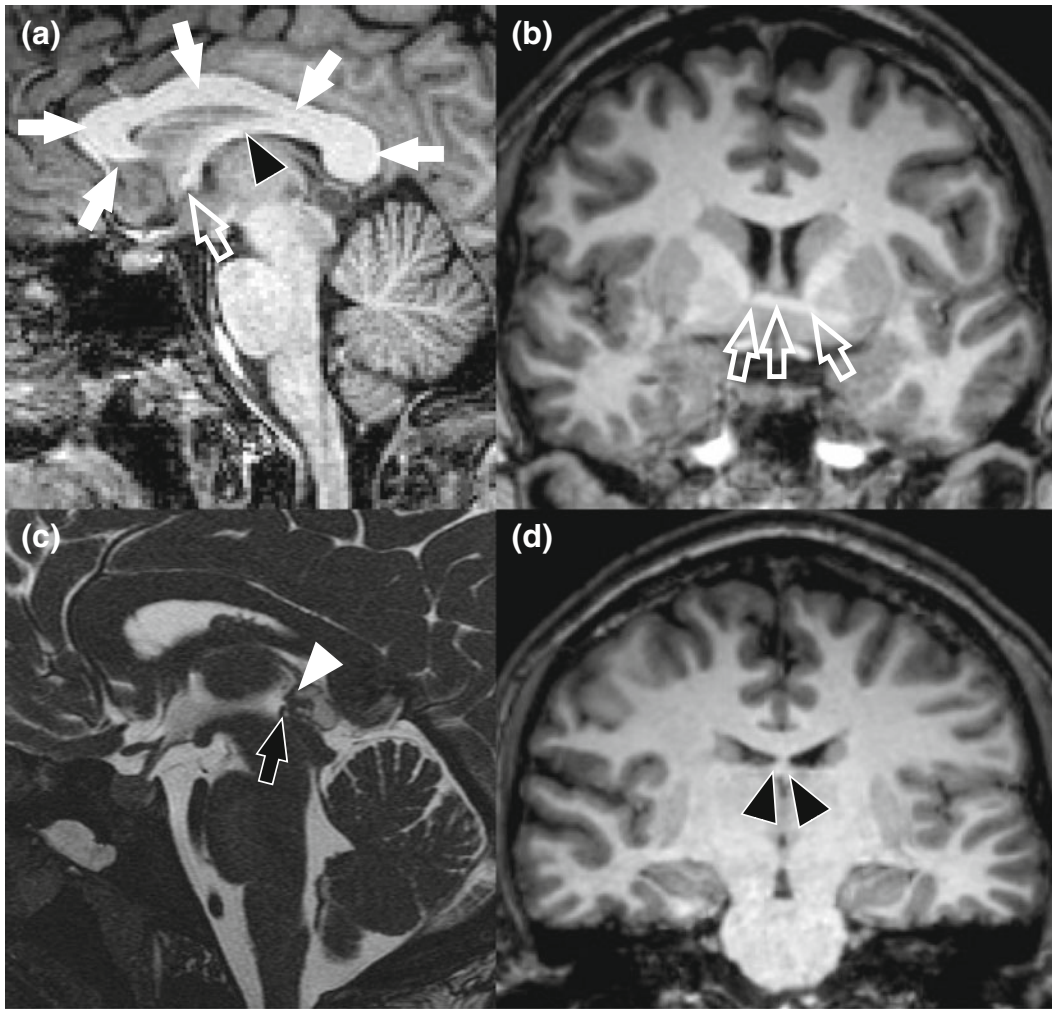

Fig. 14 Sagittal T1 (**a**), coronal T1 (**b**, **d**) and sagittal high-resolution 3d T2 (**c**). The components of the corpus callosum are named from anterior to posterior (*white arrows*) the rostrum, genu, body, isthmus and splenium. The anterior commissure (*open white arrows*, **a**, **b**) connects the two temporal lobes and can be seen immediately anterior to the fornix. The hippocampal commissure connects the fornices (*black arrowheads*, **a**, **d**). The posterior commissure (*black arrow*, **c**) and habenular commissure (*white arrowhead*, **c**) are found at the posterior margin of the third ventricle

the jugular foramen where venous blood enters the jugular veins (Fig. 21).

7 Sensory Pathways—Connecting the Spinal Cord to the Cerebral Cortex

As described elsewhere, sensory information from the periphery arrives at the medulla, via the spinal cord separated into two broad categories of modality: the spinothalamic system, carrying information regarding crude touch, pain and temperature, and the dorsal column system containing information regarding discriminatory touch, light touch/vibration and joint position sense. The spinothalamic system crosses at, or within one or two levels of entering the spinal cord so that in the medulla the right spinothalamic tract represents relevant sensory information from the contralateral, left side of the body. These are already second

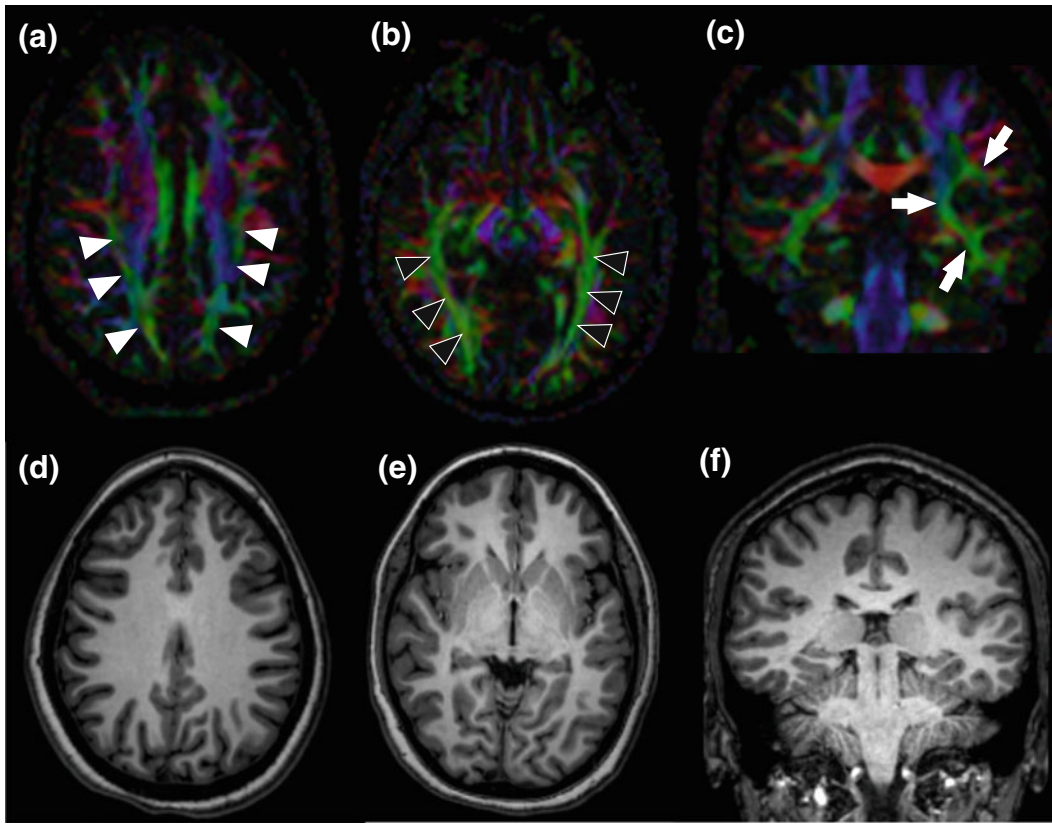

Fig. 15 Axial (**a**, **b**) and coronal (**c**) directionally encoded DTI colour maps; **d**, **e** (axial) and **f** (coronal) T1 volumes. Part of the superior longitudinal fasciculus is shown in *green* in a (*white arrowheads*) connecting the frontal and parietal lobes; the inferior longitudinal fasciculus connecting the occipital and temporal lobes is shown in *green* in **b** (*black arrowheads*). The arcuate fasciculus is shown in **c** in *green* (*white arrows*) connecting the temporal and parietal lobes

order neurones, having synapsed at, or within a few levels of entry. In distinction, the dorsal column system remains ipsilateral to the side of entry up until the level of the medulla where the first order neurones terminate on one of two nuclei—the nucleus gracilis, located medially (carrying dorsal column information from the lower half of the body) and the nucleus cuneatus, located laterally (carrying dorsal column information from the upper half of the body) (Fig. 22) [11].

The output of the nuclei gracilis and cuneatus is the medial lemniscus—these fibres now cross to the contralateral side of the brainstem in a paramedian location and are found in an anteroposterior configuration at the level of the obex of the fourth ventricle (Fig. 23).

Having crossed, the medial lemnisci ascend through the pontine tegmentum, located still near the midline, anterior to the fourth ventricle and pontine reticular formation. They are now joined by the spinothalamic tracts located laterally (Fig. 24).

As the sensory tracts ascend further into the midbrain they move more laterally, now being found near the lateral edges of the midbrain; the spinothalamic tracts rotate to take a more posterior position, still in close apposition with the medial lemnisci (Fig. 25) [2, 3, 12].

The destination of these second order neurones in the medial lemnisci and spinothalamic tracts, carrying sensory information from the body, is the ventroposterolateral (VPL) nucleus

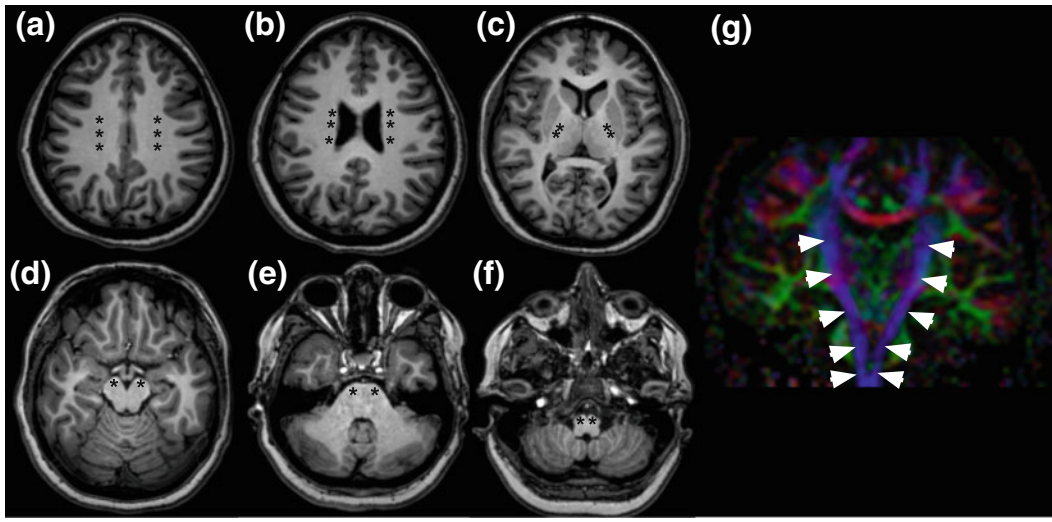

Fig. 16 Axial T1 volume showing location of the corticospinal tracts (*black asterisks*) at the level of the centrum semiovale (**a**), corona radiata (**b**), posterior limb of the internal capsule (**c**), cerebral peduncles (**d**), pons (**e**) and medullary pyramids (**f**). The tracts are outlined in *blue* (*white arrowheads*) in the coronal directionally encoded DTI map (**g**)

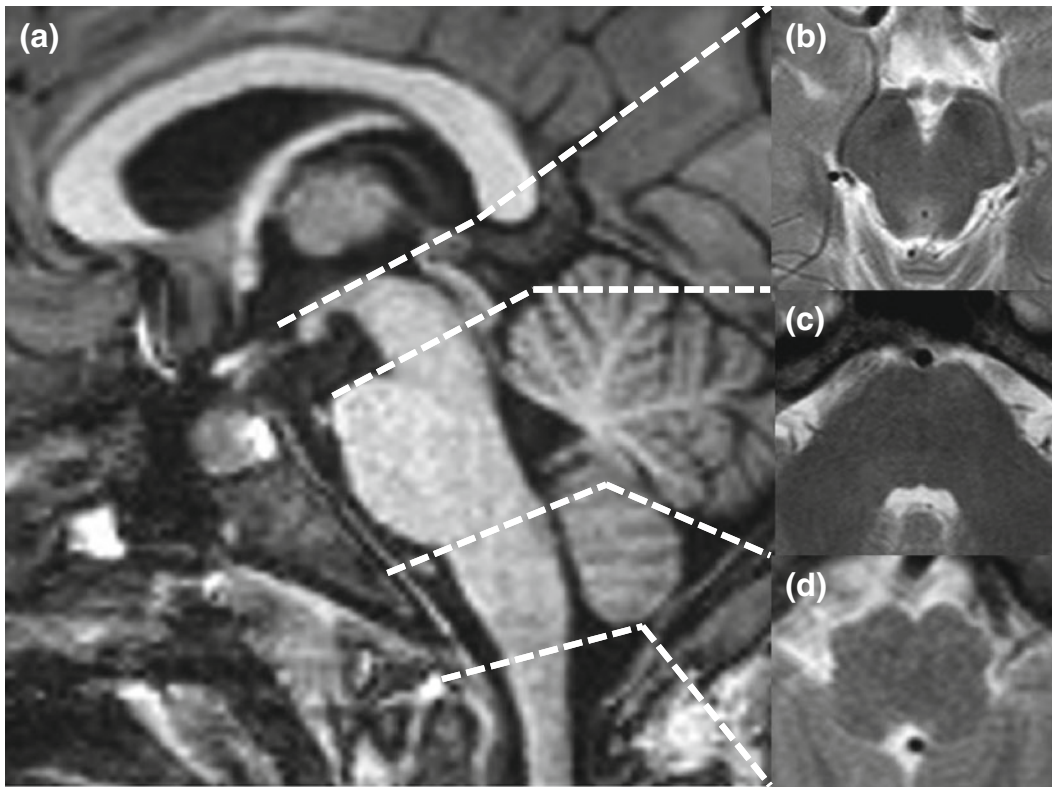

Fig. 17 Sagittal T1 volume (**a**) and axial T2 (**b**–**d**) showing components of the brainstem: the midbrain (**b**), the pons (**c**) and medulla (**d**)

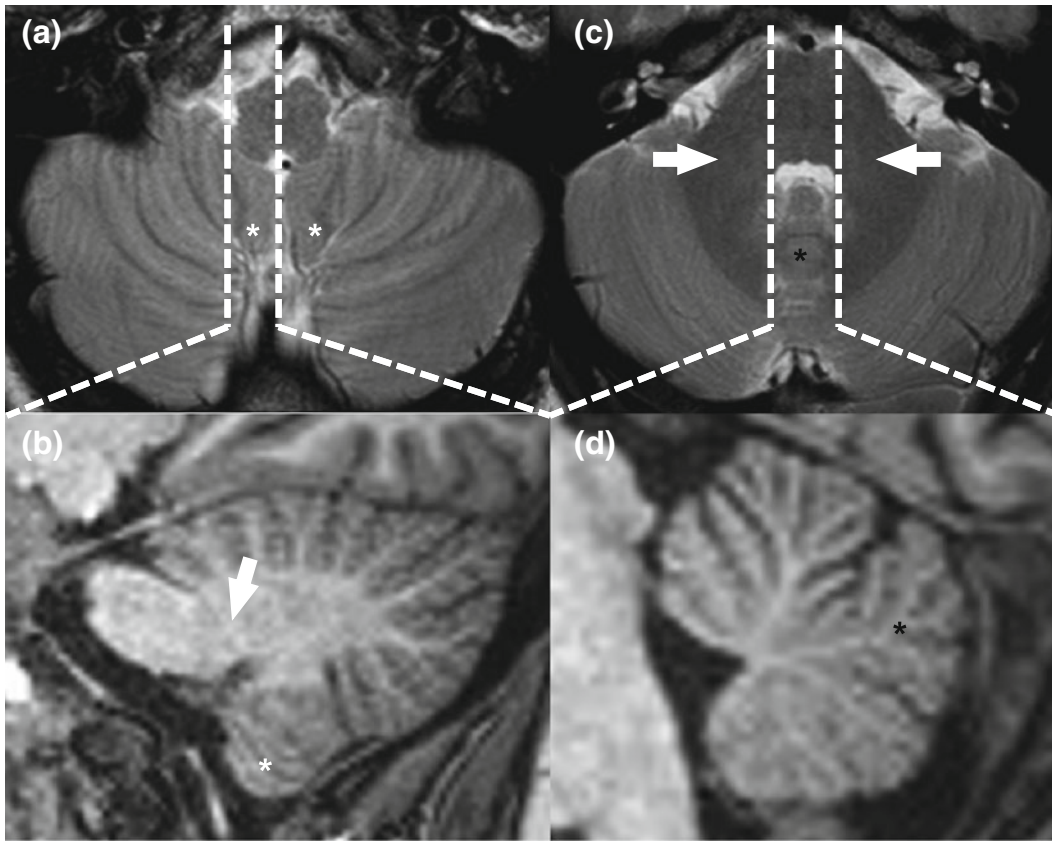

Fig. 18 Axial T2 (**a**, **c**) and parasagittal (**b**) and sagittal T1 volume (**d**) showing the cerebellar tonsils (*white asterisk*), cerebellar vermis in the midline between the two hemispheres (*black asterisk*) and the middle cerebellar peduncles (*white arrows*) connecting the cerebellum to the pons

of the thalamus (facial sensation will be described in detail subsequently) (Fig. 26).

Having synapsed in the VPL nucleus third order neurones project to the primary somatosensory cortex, located in the postcentral gyrus of the parietal lobe via the internal capsule. The posterior limb of the internal capsule, containing the somatosensory projection fibres runs between the thalamus medially and lentiform nucleus laterally (Fig. 27).

From the internal capsule, fibres project to the primary somatosensory cortex (S1), located along the postcentral gyrus in the parietal lobe. Some fibres also terminate in the secondary somatosensory cortex in the parietal operculum which will be described later, along with the somatosensory association cortex more posteriorly in the parietal lobes (Fig. 28).

The representation of the type and intensity of sensory stimuli is encoded in S1 with anatomical regions showing differing areas of activity according to the sensory homunculus. The foot is located medially, dipping down into the interhemispheric fissure, whereas the hand is located on the superior convexity; the region for facial sensation is located more inferiorly on the lateral surface (Fig. 29) [11].

8 Facial Sensation

Although the broad pattern of anatomical arrangement is the same for facial as body sensation some specific differences are highlighted, particularly given the prevalence of facial pain as a clinical problem.

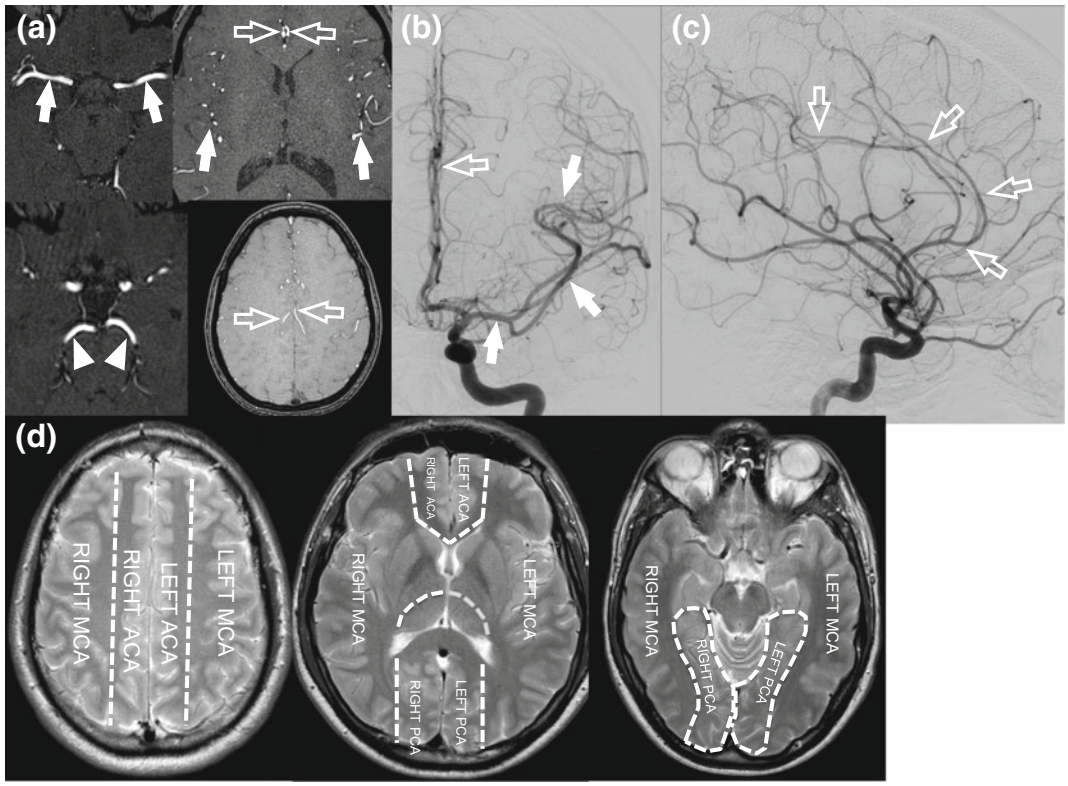

Fig. 19 Anterior circulation. Axial time-of-flight MR (**a**), anteroposterior view (**b**) and lateral view (**c**) cerebral angiogram (internal carotid artery injection) and axial T2 weighted images (**d**). The MCAs are shown by the *solid white arrows*, the ACAs by the *open white arrows* and the PCAs by the *white arrowheads*. The supratentorial vascular territories are outlined on the axial T2 weighted images

The trigeminal nerve is the main sensory nerve supplying sensation to the head/face via its three afferent branches—the ophthalmic division (V_i) covering the forehead/orbits; the maxillary division (V_{ii}) covering sensation from the mid-face and the mandibular division (V_{iii}). These join together to form the Gasserian, or trigeminal ganglion in Meckel's cave, a small continuation of the subarachnoid space from the pre-pontine cistern, medial to the temporal lobes (Fig. 30). This contains the sensory cell bodies of the sensory fibres with afferent branches extending proximally, along the cisternal portion of the trigeminal nerve to terminate on the trigeminal nucleus in the brainstem [3].

Several blood vessels are found in close proximity to the trigeminal nerve as it crosses the pre-pontine cistern/enters the pons. These are usually the superior cerebellar or anterior inferior cerebellar arteries, or sometimes a prominent petrosal vein branch. Contact, and particularly displacement, of the proximal, relatively unmyelinated portion of the trigeminal nerve (the so-called root entry zone) is associated with trigeminal neuralgia (Fig. 31) [13].

The trigeminal nucleus spans the length of the brainstem and is divided into three parts: the mesencephalic nucleus (in the midbrain), the main sensory (and adjacent motor) nucleus in the pons and the inferior extension into the medulla/upper cervical cord, called the spinal nucleus and associated tract (Fig. 32).

The mesencephalic nucleus plays a relatively small role, receiving muscular stretch information from muscles of mastication and is primarily involved in the jaw jerk reflex. The main sensory

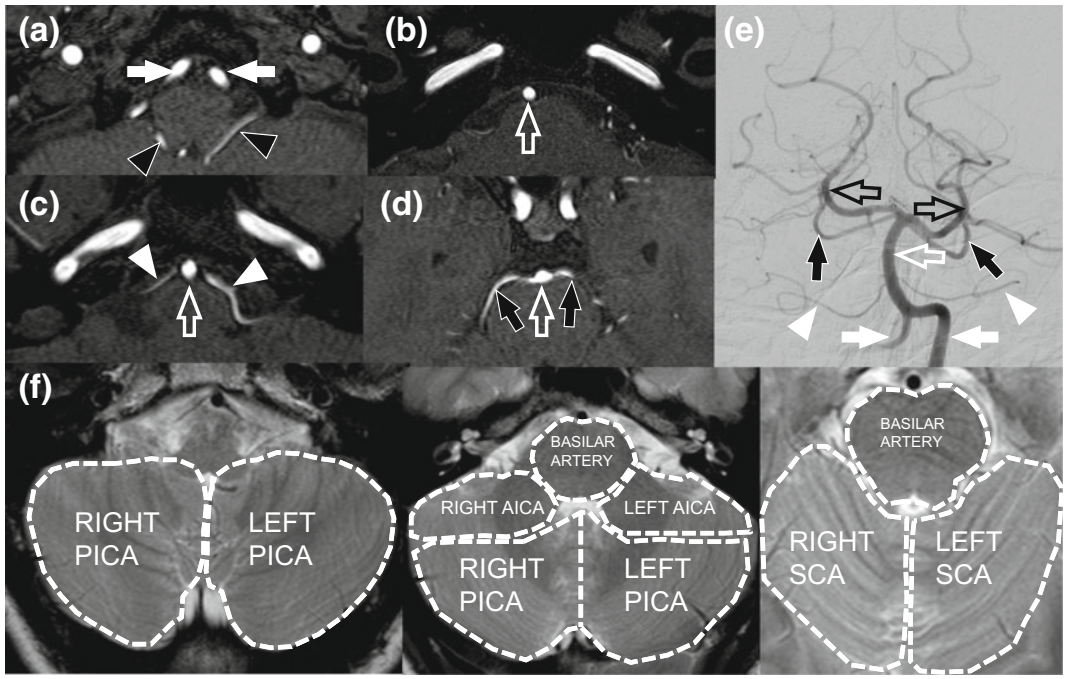

Fig. 20 Axial time-of-flight MRA at the level of the medulla (**a**), pons (**b**), pons/midbrain junction (**c**) and midbrain (**d**). AP oblique vertebrobasilar cerebral angiogram (**e**) and axial T2 weighted images with posterior fossa vascular territories (**f**). Solid white arrows show the distal vertebral arteries, *black arrowheads* show the PICAs, *open white arrow* shows the basilar artery, *white arrowheads* show the AICAs, *solid black arrows* show the SCAs, *open black arrows* show the PCAs, the terminal branches of the basilar artery

nucleus at the level of the pons is the cranial correlate of the nucleus cuneatus/gracilis in the medulla; it receives general somatosensory afferent input (i.e. light/discriminate touch, etc.) including jaw joint position sense from the ipsilateral side of the head. After synapsing efferents cross the midline as the trigeminal lemniscus and joint the medial lemniscus, ascending through the brainstem towards the thalamus. The destination nucleus in the thalamus for facial sensation is the ventroposteromedial (VPM) nucleus, located immediately adjacent to the VPL nucleus, dealing with body sensation. A small subsection of second order efferents do not cross and ascend to the ipsilateral VPM, carrying intraoral sensation, called the dorsal trigeminal tract (Fig. 33) [2, 3].

Afferent fibres containing pain and temperature information enter the pons and travel inferiorly, in the trigeminal tract to the spinal nucleus of the trigeminal nerve. Different subsections of the spinal nucleus deal with different sensory modalities but pain and temperature in particular are dealt with by the most inferior 'caudal' nucleus, which can extend down as far as the C3–4 segment. After synapsing, second order neurones cross to the contralateral ascending spinothalamic tract and then travel superiorly to the VPM nucleus of the contralateral thalamus (Fig. 34) [2].

9 Other Cranial Nerves with Sensory Components

In addition to specialist sensory information (e.g. taste), there is a contribution to general and pain sensation, in particular around the ear/external auditory canal from the facial (VIIth), glossopharyngeal (IXth) and vagus (Xth) nerves. Sensory afferent fibres from all these nerves synapse on the spinal trigeminal nucleus and tract and form second order neurone connections

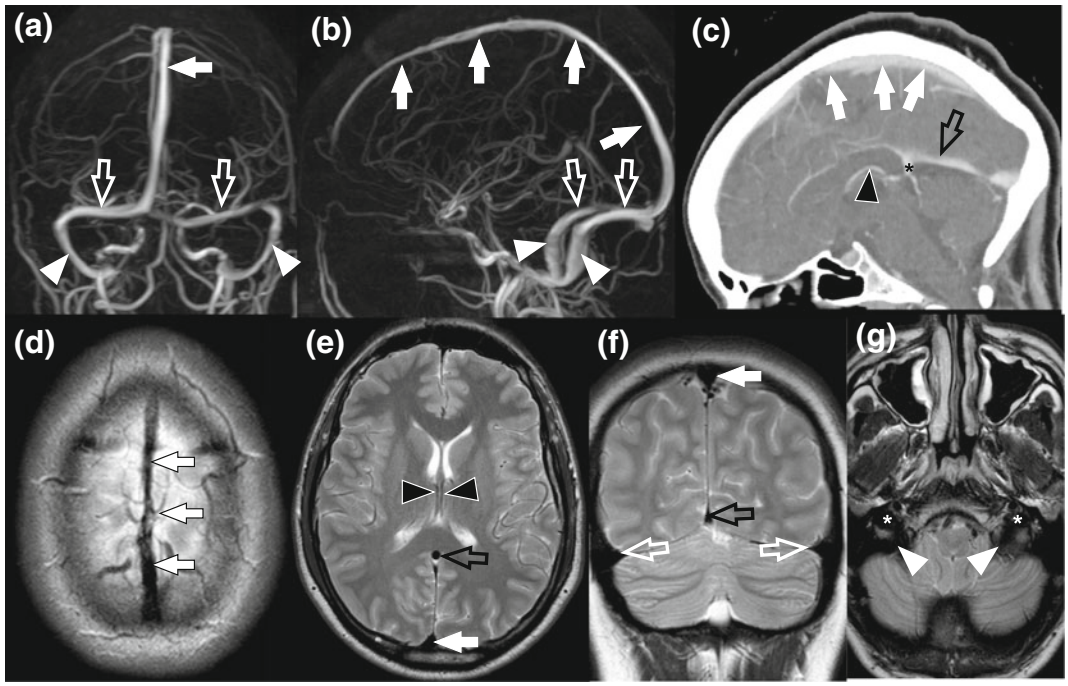

Fig. 21 Cerebral venous system. Phase contrast MR venogram (**a**), AP maximum intensity projection (**b**), lateral maximum intensity projection (**c**), sagittal CT venogram (**d**, **e**, **g**), axial T2 weighted images (**f**), coronal T2 weighted image. *Solid white arrow* Superior sagittal sinus; *open white arrow* transverse sinuses; *white arrowheads* sigmoid sinuses; *open black arrow* straight sinus; *black arrowheads* internal cerebral veins; *black asterisk* vein of Galen; *white asterisk* jugular foramen

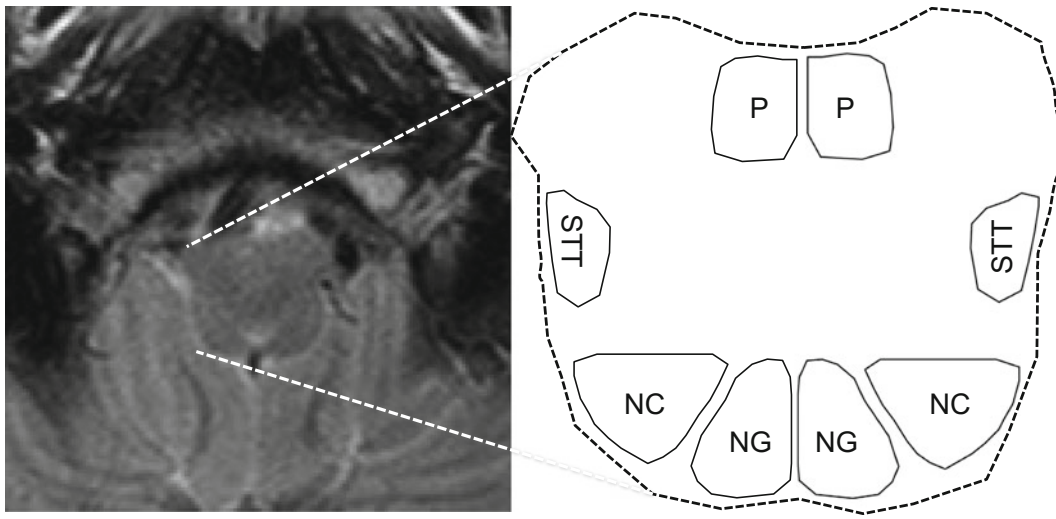

Fig. 22 Axial T2 weighted image with schematic drawing showing the relative positions of the dorsal column nuclei (*NG* Nucleus gracilis, *NC* nucleus cuneatus), the spinothalamic tracts (*STT*) and the corticospinal tracts in the medullary pyramids (*P*)

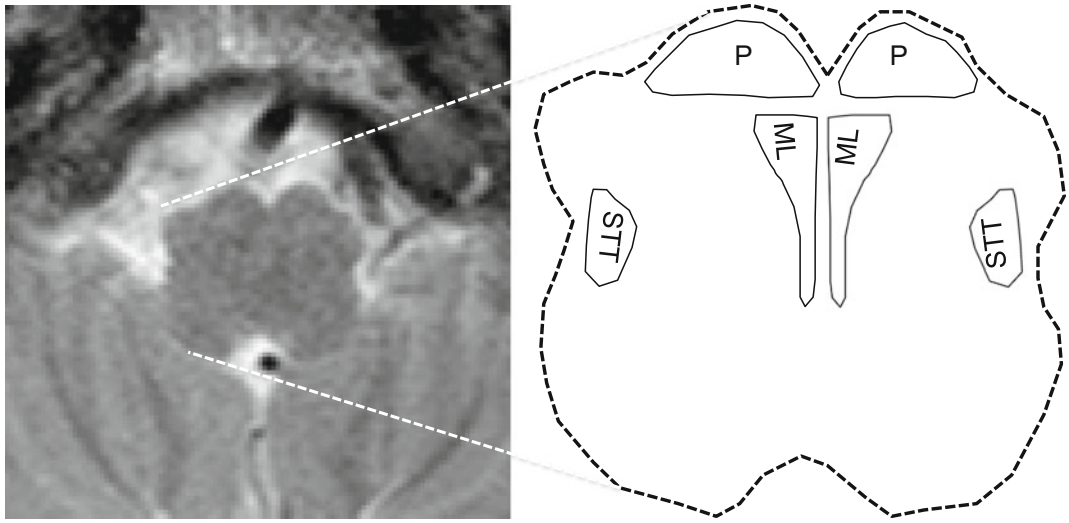

Fig. 23 The medullary pyramids (*P*) are easier to identify anteriorly. The spinothalamic tract (*STT*) remains located laterally. The medial lemnisci (*ML*) have formed in the midline as the outflow tract of the nucleus gracilis and cuneatus

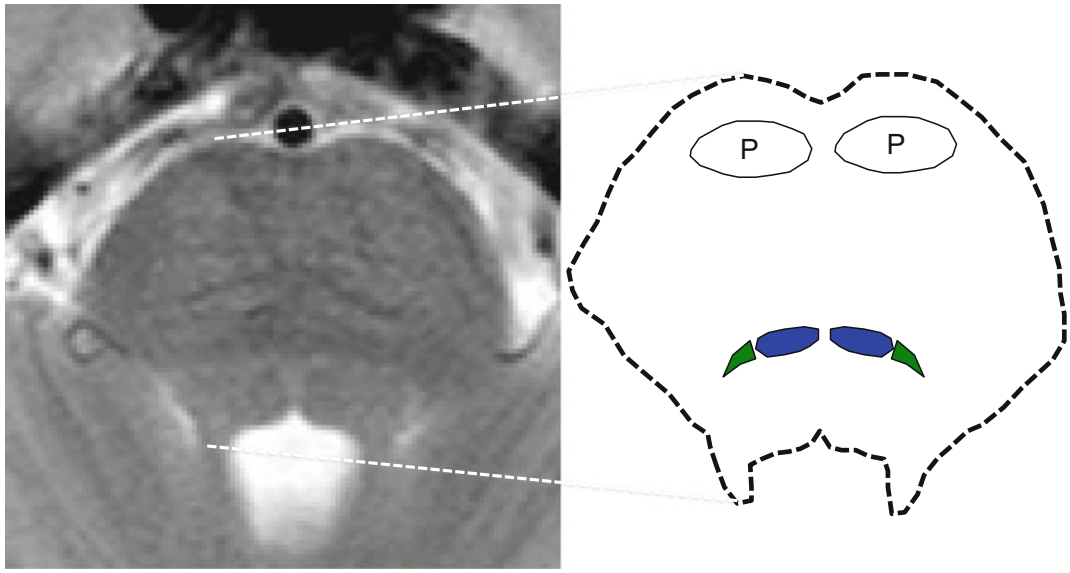

Fig. 24 The corticospinal tracts (*P*) are located in the anterior pons. The medial lemnisci (*blue*) have are now joined laterally by the spinothalamic tracts (*green*) in the pontine tegmentum

as described for the trigeminal nerve above. The more 'vague' visceral efferent fibres (e.g. sensation from mucous membranes in the gut, pharynx, larynx etc.) as well as taste information terminate in a different brainstem nucleus called the nucleus (and tract) of solitarius, located in the dorsomedial medulla at the level of the pyramids (Fig. 35) [14]:

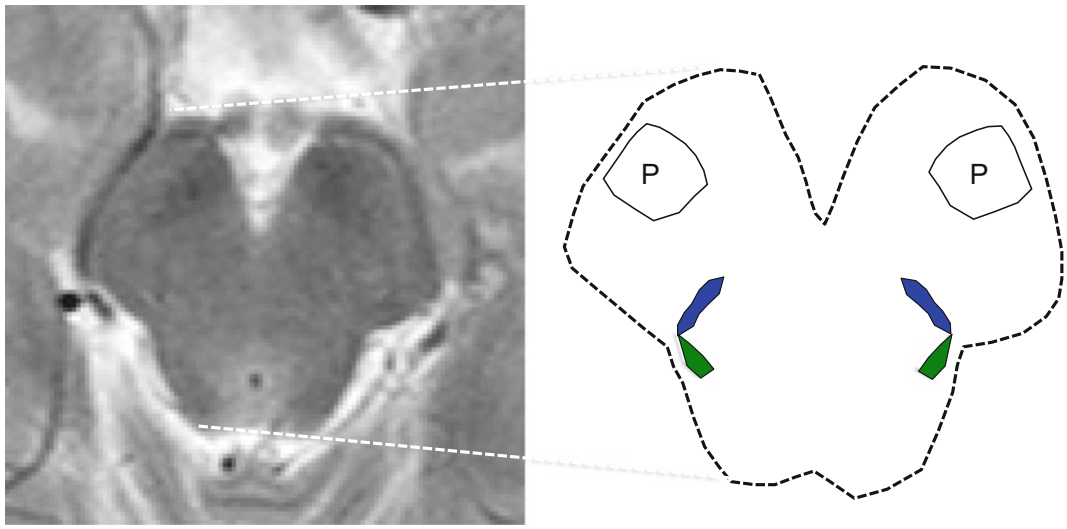

Fig. 25 The location of the corticospinal tracts (*P*) is shown in the cerebral peduncles. The medial lemnisci (*blue*) and spinothalamic tracts (*green*) are now positioned more dorsolaterally

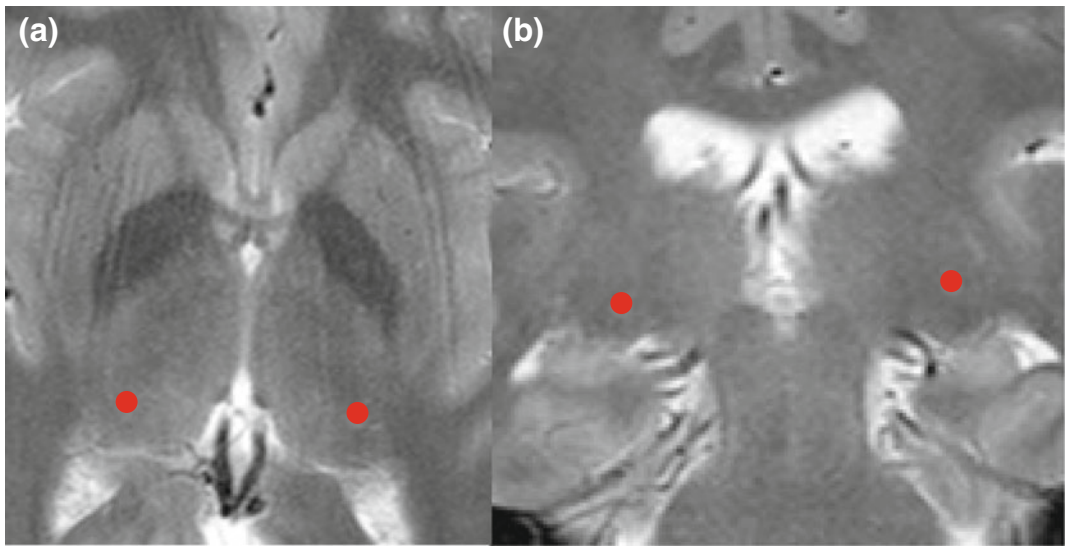

Fig. 26 Axial (**a**) and coronal (**b**) T2 weighted images showing the location of the ventral posterolateral (VPL) nucleus of the thalamus shown by the *red circles*

10 Brainstem Interactions of the Ascending Sensory System

The brainstem contains a multitude of nuclei, situated in the tegmentum—the tissue ventral to the fourth ventricle and cerebral aqueduct. Although difficult to identify on standard neuroimaging the approximate location is shown in Fig. 36.

The nuclei are interspersed with many ascending and descending pathways making multiple different connections and having many different functions. The group together are referred to as the reticular formation. The reticular formation receives direct input from the ascending, uncrossed

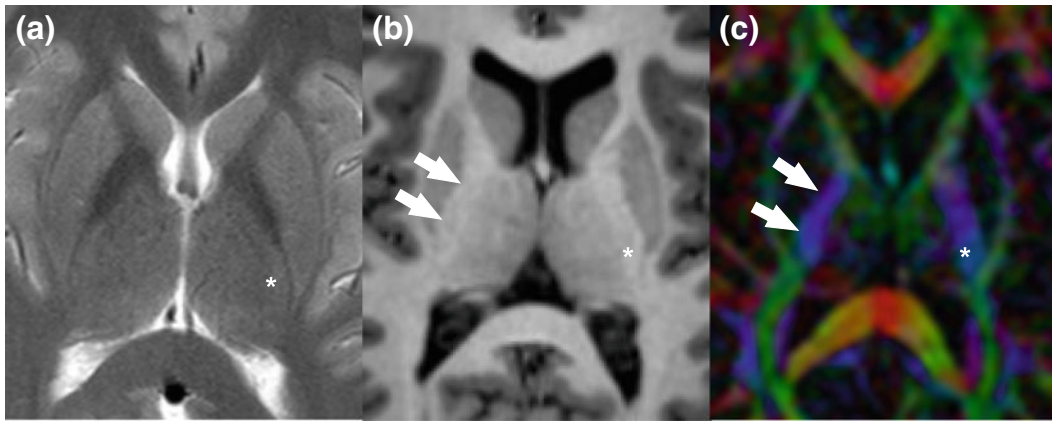

Fig. 27 Axial T2 (**a**), T1 volume (**b**) and directionally encoded colour FA map (**c**) showing the location of the somatosensory projection (*white asterisk*) in the posteriormost aspect of the posterior limb of the internal capsule (*white arrows*)

spinotectal tract—and have two output tracts—the medial (originating in the pons) and lateral (originating in the medulla) reticulospinal tracts. This output keeps spinal reflex arcs in a state of tonic inhibition but may facilitate reflexes such as withdrawal at a subconscious level in response to a painful stimulus [2, 3, 11].

The reticular formation alerts the brain to the presence of a potentially noxious stimulus via the reticulothalamic pathway—uncrossed neurones that pass from the reticular system to the intralaminar nuclei of the thalamus (see later). The reticular formation and intralaminar thalamic nuclei are together referred to as the reticular activating system (RAS).

Ascending spinothalamic tract fibres also synapse with a variety of other brainstem/diencephalic structures in a combination of three tracts that are phylogenetically older than the 'direct' anterolateral spinothalamic system and sometimes referred to as the paleospinothalamic pathway [11]. The spinotectal tract is crossed at the level of entry to the spinal cord and terminates in the region of the superior colliculus (tectal plate of the midbrain) and serves to turn the head and eyes in the direction of the stimulus (Fig. 37).

The spinohypothalamic pathway also crosses with the spinothalamic tract near/at the level of spinal cord entry and activates the autonomic reflex responses to noxious stimuli, such as elevating the heart rate and blood pressure (Fig. 38).

The third component of the paleospinothalamic pathway is the spinomesencephalic tract. This is also a crossed component of the ascending spinothalamic tract that terminates in the midbrain periaqueductal grey matter (PAG). A small component also terminates on the adjacent parabrachial nucleus of the midbrain which has outputs directly to the amygdala involved in the emotional response to pain (Fig. 39) [15].

The function of the PAG is thought to lie in the modulation of ascending pain information. The PAG is another structure that is difficult to identify on standard neuroimaging but forms a horseshoe of grey matter ventral and lateral to the cerebral aqueduct in the midbrain (Fig. 40).

In response to spinothalamic input the PAG can produce an inhibitory effect on transmission through the spinothalamic system at the level of the dorsal horn/entry level in the spinal cord. Fibres run inferiorly from the PAG to the nucleus raphe magnus, a serotonergic midline pontine raphe nucleus whose output runs inferiorly through the spinal cord and inhibits transmission of painful sensory input in the dorsolateral spinal cord (Fig. 41) [16].

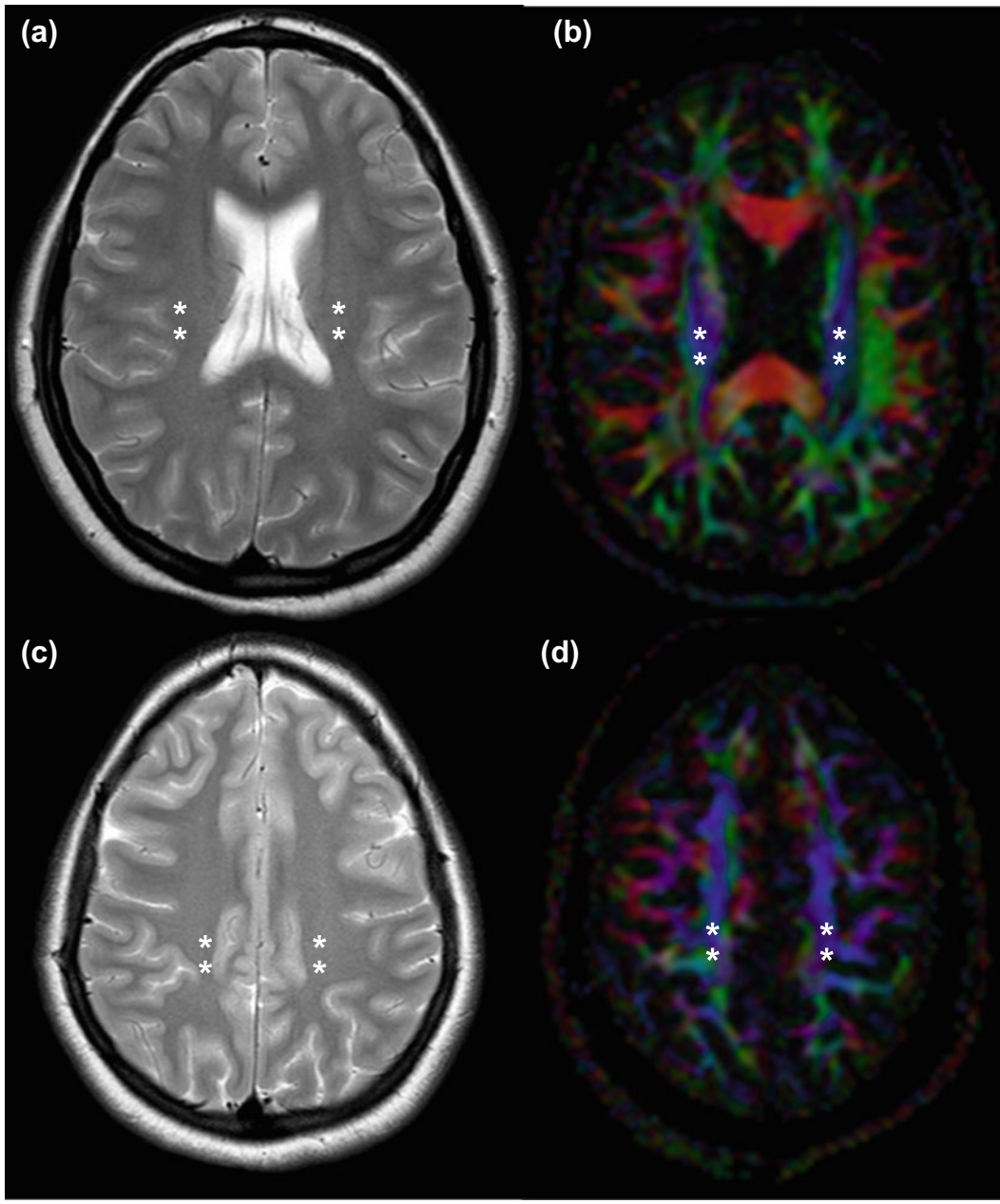

Fig. 28 Third order neurons (*asterisks*) project from the VPL nucleus of the thalamus to the primary somatosensory cortex via the corona radiata (axial T2, **a** and colour-coded FA map, **b**) and centrum semiovale (axial T2, **c** and colour-coded FA map, **d**)

The PAG is known to receive many ascending sensory inputs and also descending input from the supratentorial brain. Similarly there are many reciprocal outputs back to the reticular formation and also superiorly back to the supratentorial brain, amygdala and hypothalamus. It would appear the PAG has an integrative role in influencing via balance of outputs the

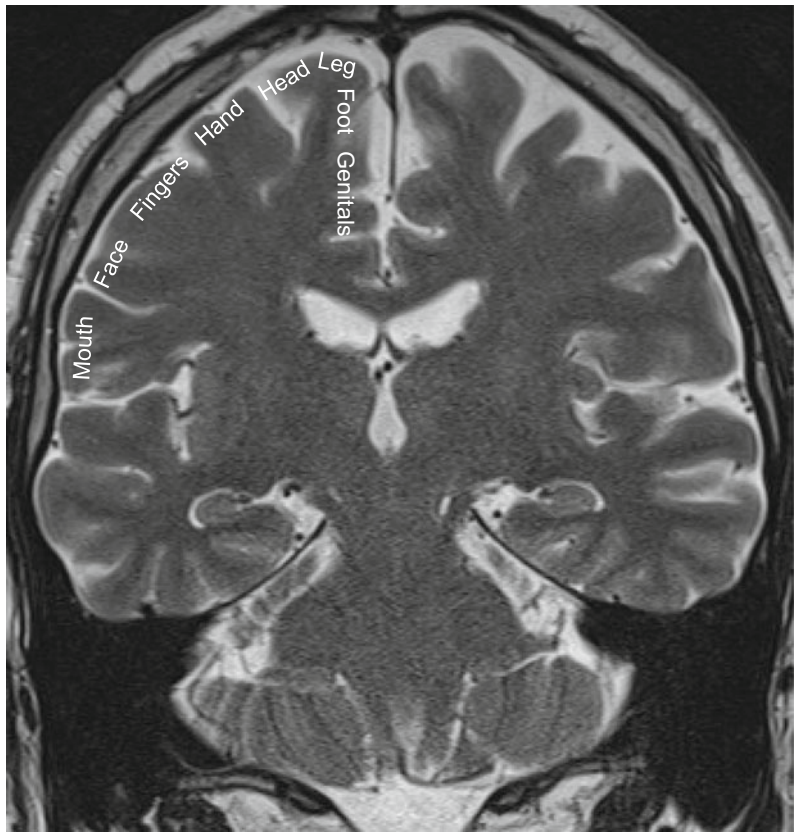

Fig. 29 Coronal T2 weighted images through the postcentral gyrus showing the primary somatosensory cortical homonculus—i.e. the approximate distribution of regions of cortical sensation by body part

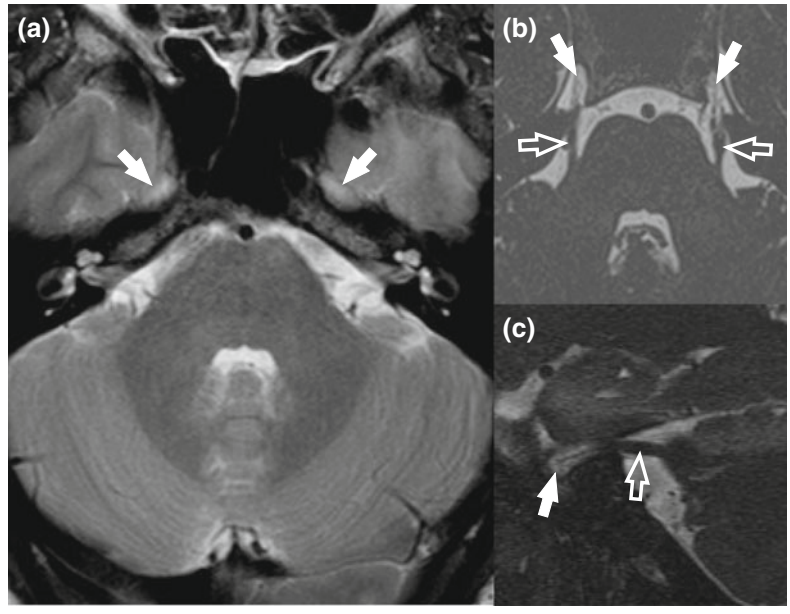

Fig. 30 Axial T2 (**a**), high-resolution 3d T2 axial (**b**) and sagittal (**c**) showing CSF in Meckel's cave (*white arrow*). The cisternal portions of the trigeminal nerve can be seen crossing the pre-pontine cistern from the pons (*open white arrow*)

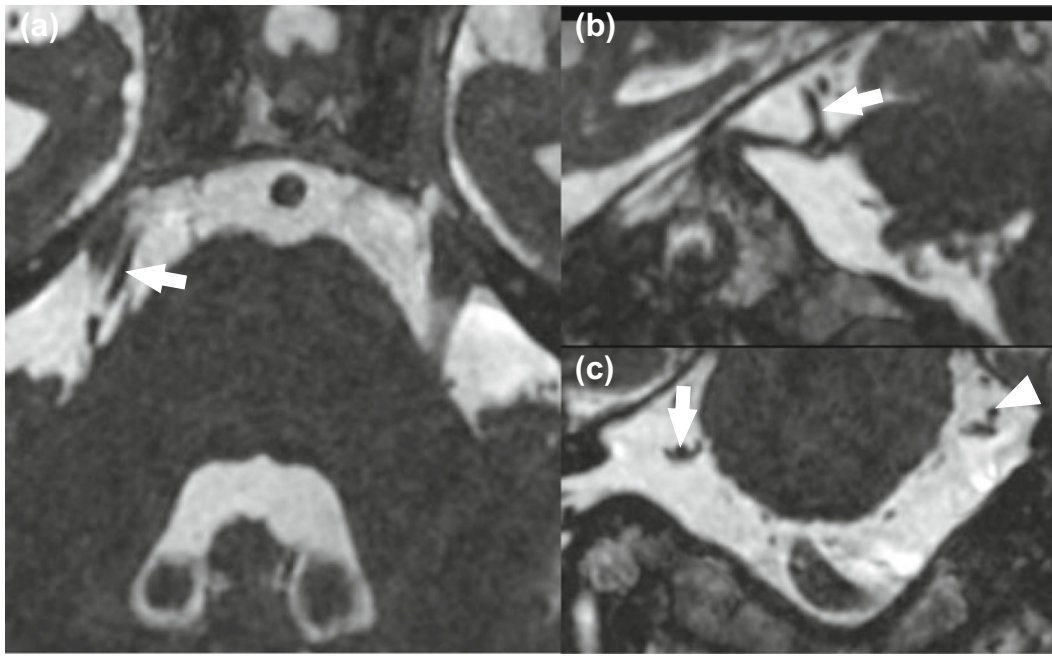

Fig. 31 Axial (**a**), sagittal (**b**) and coronal (**c**) 3d T2 weighted images in a patient with right-sided trigeminal neuralgia showing compression of the cisternal portion of the right trigeminal nerve by the right superior cerebellar artery (*white arrow*); compare to the normal appearance on the left side (*white arrowhead*)

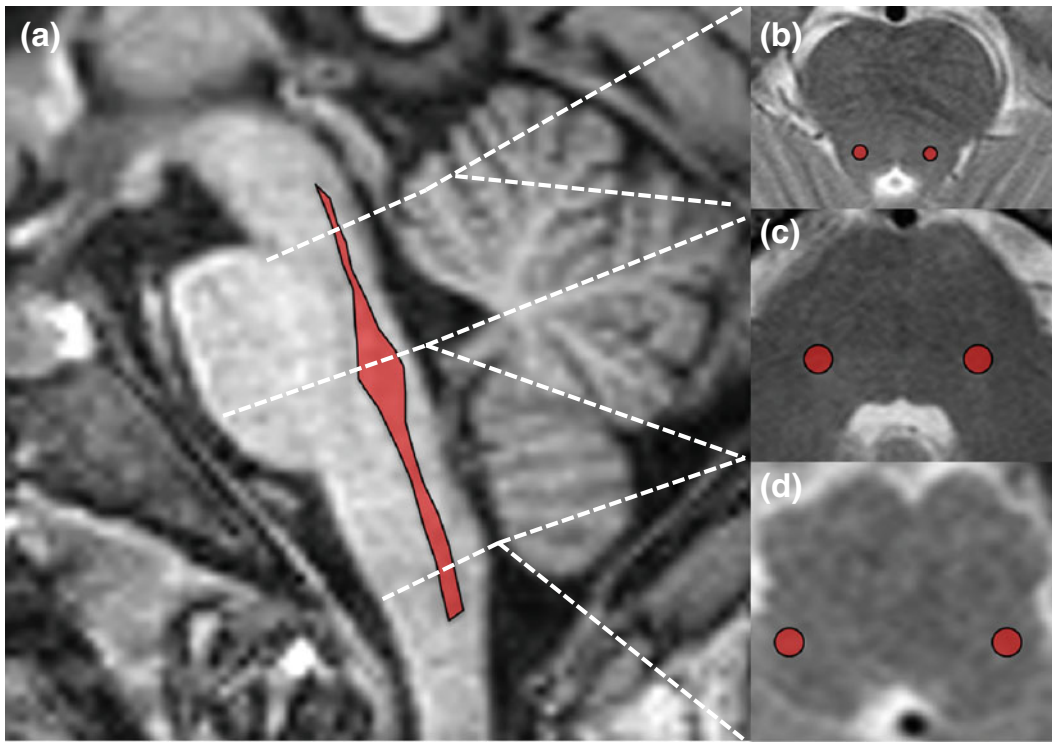

Fig. 32 Sagittal T1 volume (**a**) showing one of the spinal trigeminal nuclei (*red*) with corresponding axial T2 images at level of the mesencephalic nucleus (**b**), main sensory nucleus (**c**) and spinal nucleus (**d**) which are all in continuity

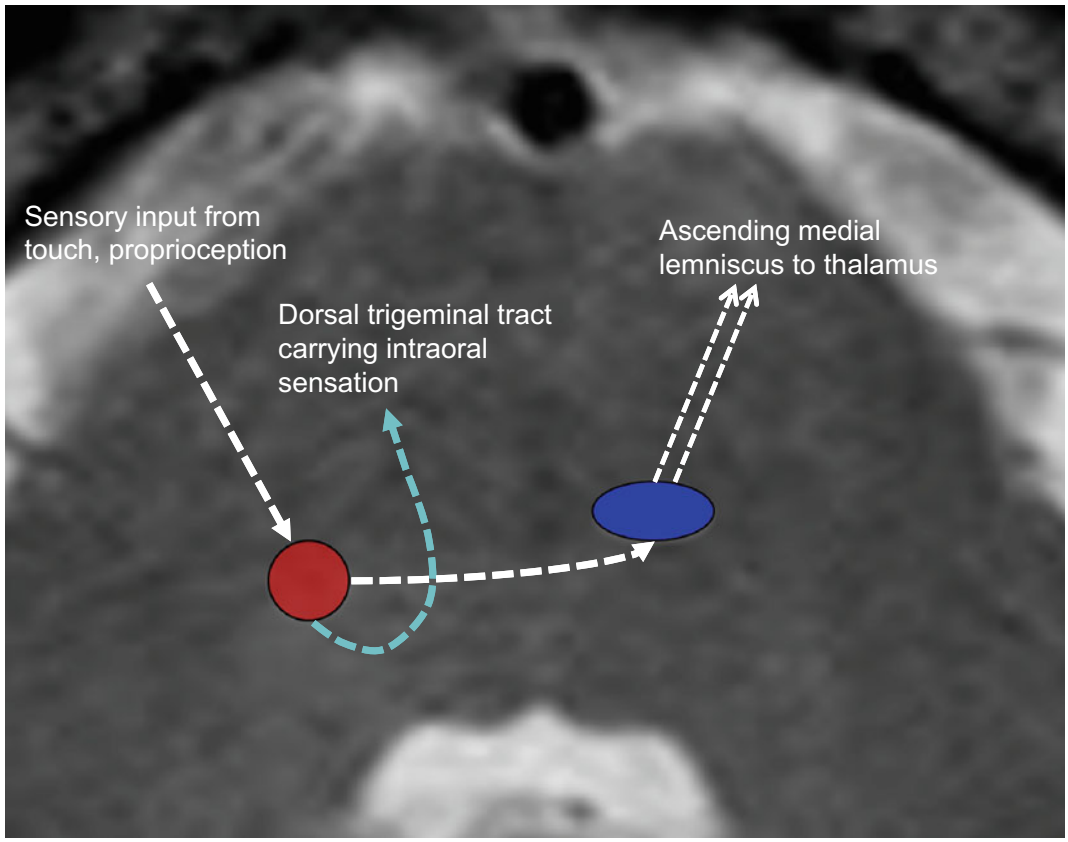

Fig. 33 Light touch and proprioception information synapses in the main sensory nucleus in the pons. 2nd order neurons mainly cross to join a subsection of the contralateral medial lemniscus called the trigeminal lemniscus to ascend to the thalamus. A small subgroup carrying intraoral sensation remain ipsilateral and ascend as the dorsal trigeminal tract heading for the ipsilateral VPM nucleus in the thalamus

fight-or-flight response to a threat. There are connections with the locus ceruleus in the upper pons which is one of the main norepinephric outputs back to the hypothalamus, thalamus and supratentorial brain; downward norepinephric modulation of spinal pain sensation transmission comes from the lateral reticular formation in the medulla (Fig. 42) [2].

Several nociceptive pathways also terminate in the cerebellum (the cuneocerebellar tract, the dorsal, ventral and rostral spinocerebellar tracts). As these pathways are primarily concerned with the subconscious maintenance of body posture they will not be considered further.

11 The Thalamus

The thalami are collections of deep grey matter nuclei situated deep within the brain, either side of the third ventricle. They act as a relay station for tracts both ascending from the spinal cord to the cortex, and vice versa from the cortex to the thalamus, back to the cord and other parts of the brain. The internal structure of the thalamus is not appreciable on routine neuroimaging but by understanding a schematic diagram this can be applied to anatomical imaging allowing at least approximate locations of individual nuclei to be extrapolated.

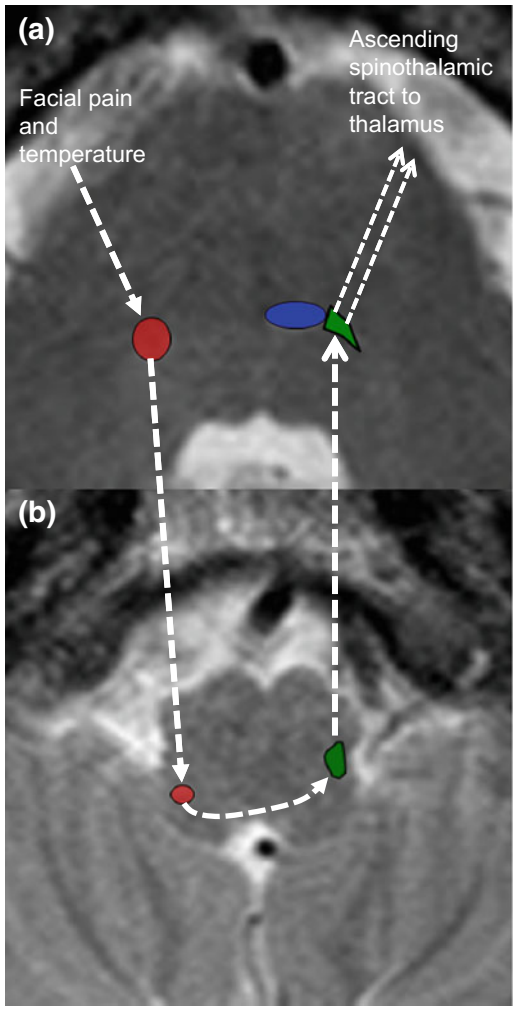

Fig. 34 Axial T2 images at the level of the pons (**a**) and medulla (**b**). Pain and temperature enters main sensory nucleus and descends to the ipsilateral spinal nucleus in the medulla where they synapse. 2nd order neurons cross to the contralateral spinothalamic tract (*green*) and ascend to the contralateral thalamus

The thalamus is made up of different groups of nuclei, separated by internal structures called 'laminae'. The internal laminae form a 'Y' shape with the anterior group of nuclei in between the fork of the Y and the medial and lateral groups situated either side of the stem (Fig. 43) [2, 11, 17, 18].

The different groups can also be divided into ventral and dorsal 'tiers' or layers. The primary nuclei involved in the sensory system are the ventral posteromedial and lateral nuclei (subtending sensation of the face and body respectively), located in the ventral tier of the lateral group of thalamic nuclei (Fig. 44).

Other thalamic nuclei have other specific cortical connections—for example the ventral anterior and lateral nuclei are part of the motor pathways connecting the motor cortex, basal ganglia and cerebellum; the medial and lateral geniculate nuclei form part of the auditory and visual pathways respectively. Other nuclei have a less specific output with wide-ranging connections to many different regions of the ipsilateral cerebral hemisphere. This is particularly the case with the intralaminar nuclei—nuclei found within the laminae that separate the main groups of thalamic nuclei. The largest, the centromedian nucleus and smaller parafascicular nucleus, are located medial to the VPL and VPM nuclei. These intralaminar nuclei receive input from the spinoreticular formation in the brainstem and can be considered the superior extension of reticular activating system itself within the thalamus. From here efferents are found to the corpus striatum (caudate and putamen), the primary and secondary somatosensory cortices and the insula/cingulate cortex (Fig. 45) [2].

The medial group of thalamic nuclei—the dorsomedial nucleus and laterodorsal nucleus in particular have extensive projections to the prefrontal cortex (particularly dorsolateral prefrontal cortex, orbitofrontal cortex) and parts of the limbic system, receiving afferent inputs from the amygdala (which itself is a target for output from the parabrachial nucleus in the midbrain, part of the spinomesencephalic pain pathway).

12 Cortical Regions Involved in the Pain Perception

The primary regions involved in sensation are the primary and somatosensory cortices (SI and SII). S1 is located in the posterior surface of the central sulcus, extending onto the cortical surface of the postcentral gyrus. This extends all the way down the postcentral gyrus from the medial

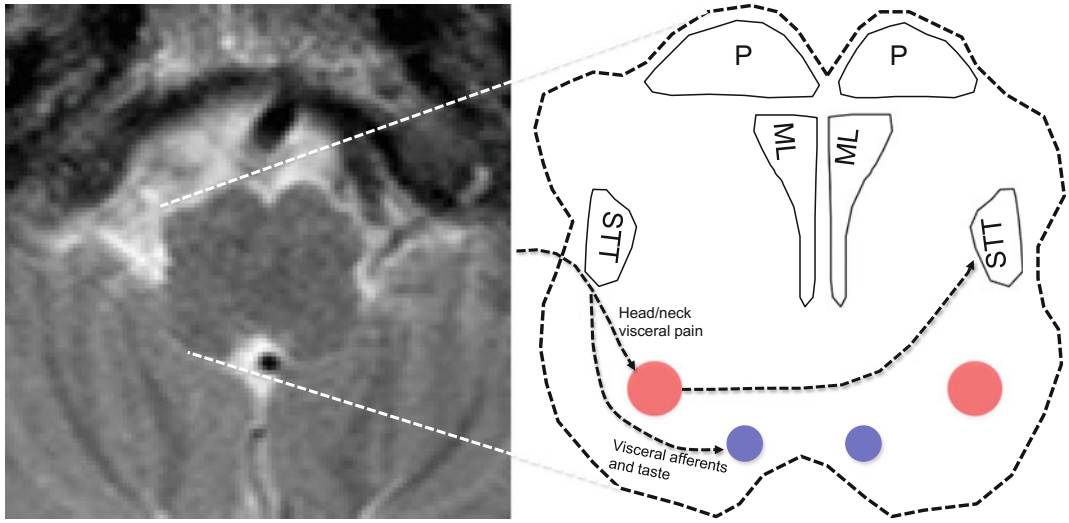

Fig. 35 Axial T2 and schematic of the medulla. Glossopharyngeal and vagus sensory afferents. Pain fibres synapse on the spinal trigeminal nucleus (*red circle*) from which fibres cross to the contralateral spinothalamic tract (STT) to ascend to the thalamus. Visceral afferents and taste information synapse on the nucleus/tract of solitarius (*blue circle*)

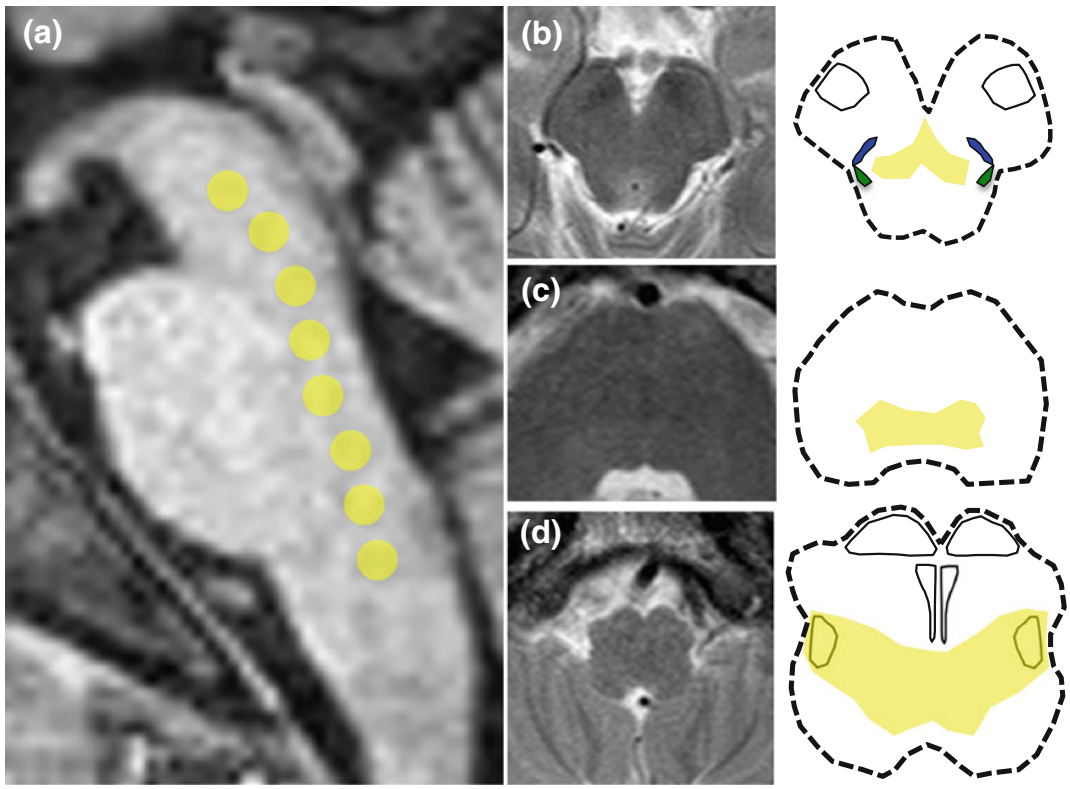

Fig. 36 Sagittal T1 volume (**a**), axial T2 at the level of the midbrain (**b**), pons (**c**) and medulla (**d**) with adjacent schematic showing the distribution of tegmental nuclei in *yellow*

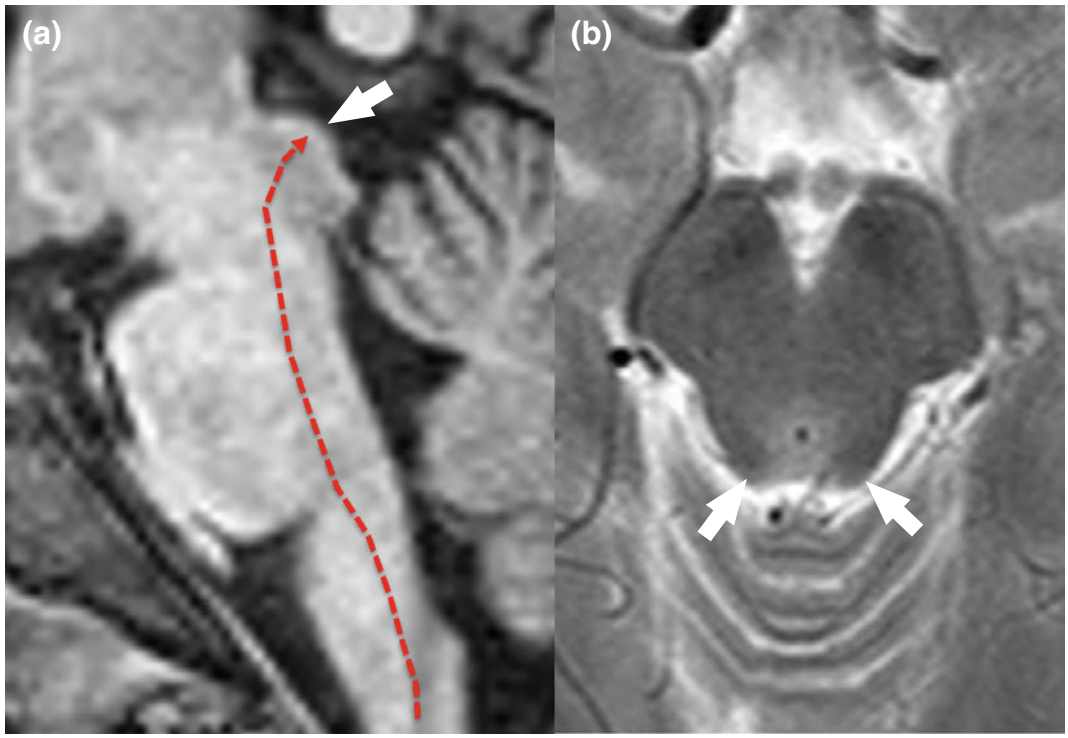

Fig. 37 Sagittal T1 volume (**a**) and axial T2 (**b**) showing position of the spinotectal tract terminating in the superior colliculus (*white arrows*). This serves to turn the head/gaze towards a painful stimulus

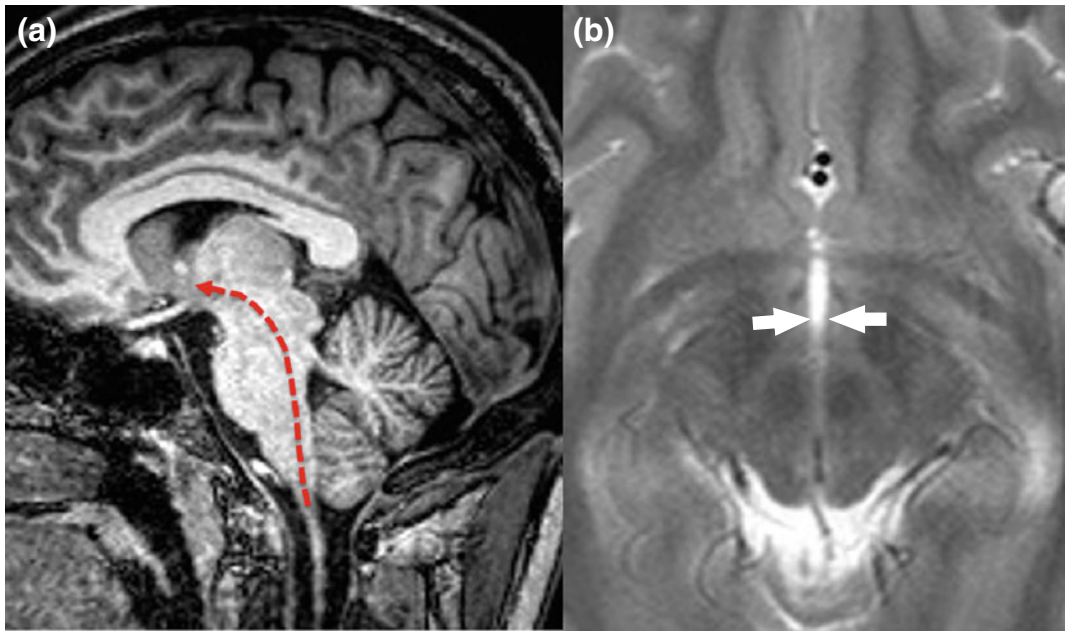

Fig. 38 Sagittal T1 volume (*left*, **a**) and axial T2 (*right*, **b**) showing the course of the spinohypothalamic tract (*dashed red line*). The hypothalamus is a collection of grey matter nuclei found lining the anterior inferior third ventricle (*white arrows*, **b**)

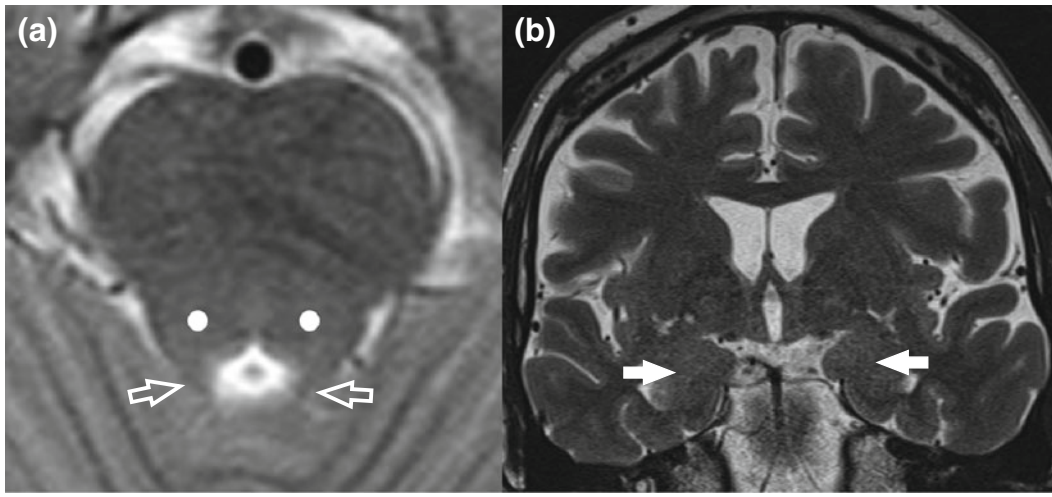

Fig. 39 Axial T2 (**a**, *left*) and coronal T2 (**b**, *right*) showing the position of the parabrachial nuclei in the brainstem (*white circles*) at the level of the superior cerebellar peduncles (*open white arrows*). These have bidirectional connections with the amygdalae (*white arrows*). Part of the spinomesencephalic tract terminates in the parabrachial nuclei and stimulate the amygdalae contributing to the emotional aspects of pain sensation. The parabrachial nuclei are also intimately connected with the respiratory nuclei in the pons

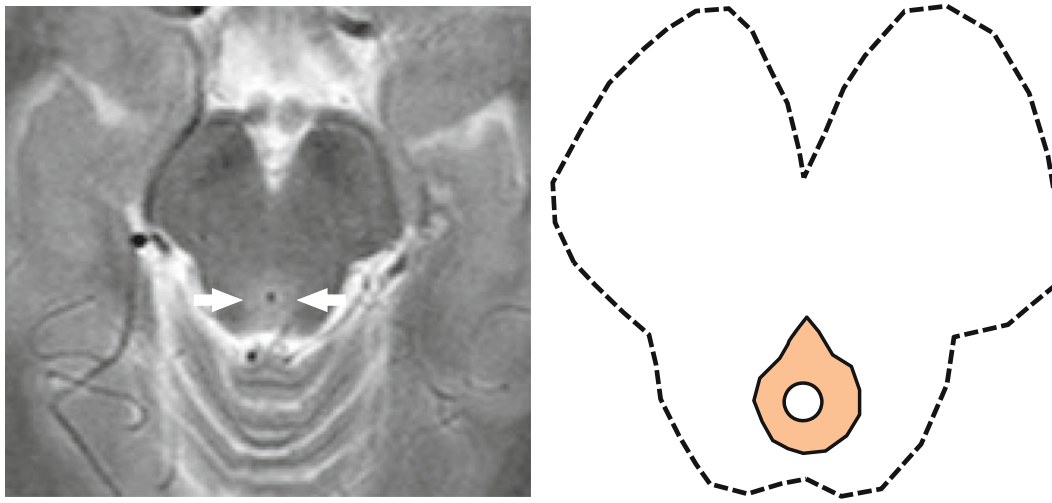

Fig. 40 Axial T2 image (*left*) and schematic (*right*) at the level of the midbrain showing position of the periaqueductal grey matter (*white arrows*)—shown in *orange* surrounding the cerebral aqueduct on the schematic image

interhemispheric fissure to the inferiormost aspect just above the lateral/posterior part of the Sylvian fissure (Fig. 46) [19].

SII is located at the inferiormost part of the postcentral gyrus, extending onto the superior surface of the superior temporal gyrus (Fig. 47).

SI is though to be involved in the detection of location and character of sensory stimulus with additional fine discriminatory functions such as the ability to identify an object via touch (stereognosis), whereas SII is thought to be more involved in memory aspects of sensory input.

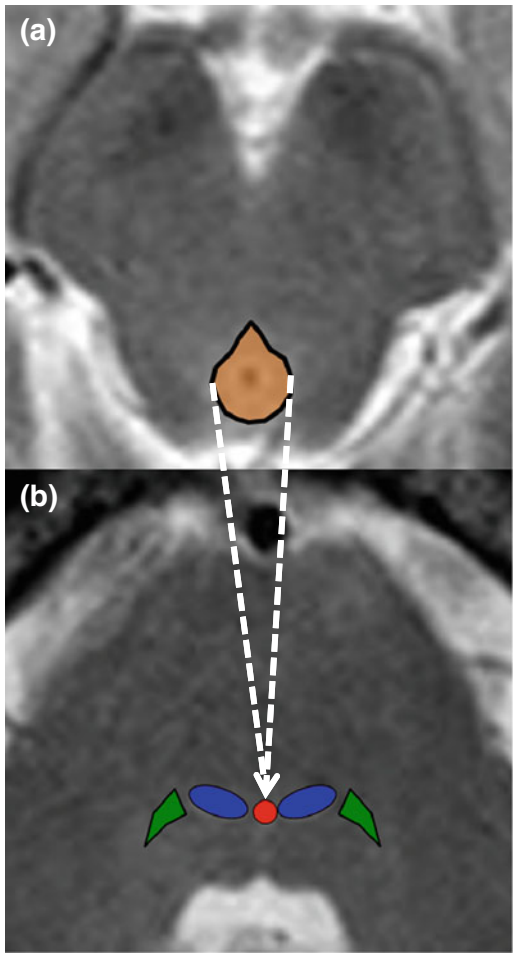

Fig. 41 Axial T2 weighted images at the level of the midbrain (**a**) and pons (**b**) showing the periaqueductal grey in *orange* (**a**) with output down on to the nucleus raphe magnus (*red circle*) in the pons. The medial lemniscus (*blue*) and spinothalamic tracts (*green*) are shown on either side

Perception of pain occurs both in SI where its character is appreciated but also/simultaneously in the anterior cingulum and insular cortices, via projection from the medial and intralaminar thalamic nuclei (Fig. 48) [20].

More recent, detailed fMRI work has shown that painful stimuli involve all areas of the insula and parietal operculum (SII) whereas other, non-noxious stimuli such as heat and cold discrimination may involve subregions of the SII and insular respectively [21].

13 Influence of Higher Order States on Pain Processing

It is well known that different emotional states can influence the experience of painful stimuli, with low mood being associated with enhanced pain perception, independent of the severity of the stimulus. Similarly, the degree to which one pays attention to painful stimuli can dramatically affect the degree to which pain is perceived; consider the professional ballet dancer who is able to 'ignore' painful sensations from the feet, or soldiers who are able to continue to fight in battle despite being severely injured. Recent functional MRI work has started to elucidate the neuroanatomical basis for these so-called 'attention/salience' networks and those involved in emotional states [22, 23].

The attention network appears to have two separate modes with a voluntary, or goal-directed mode operated by the cortex in the superior parietal lobes (Brodmann area 7) and frontal eye fields (Fig. 49). These functions are represented bilaterally—i.e. in both cerebral hemispheres [24].

A second, stimulus-driven network is right-lateralised and appears to reside in the inferior frontal lobe and inferior parietal lobule/superior temporal gyrus (Fig. 50).

Whilst these areas of the brain were primarily initially described in relation to visual attention, subsequent studies have shown they are also active in attending to other sensory inputs, including painful stimuli. It would appear that they affect the perception of pain through changing (either up or downregulating) activity in the ascending thalamocortical pain pathways. Recent work has shown positive correlation of activity between the superior parietal cortex

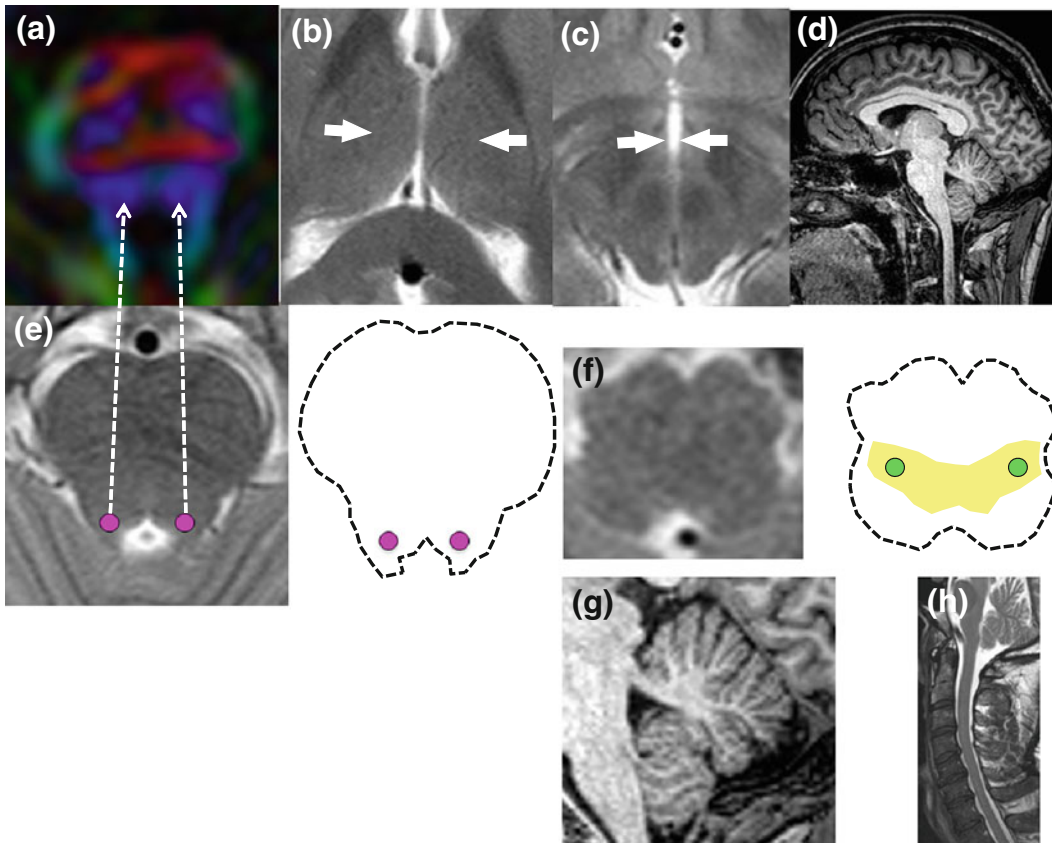

Fig. 42 Norepinephric pathways in the brain. The locus ceruleus (*pink circles* on axial T2 and graphic, **e**) is the origin of norepinephric neurons which pass superiorly up the central tegmental tracts (axial colour DTI map, *arrows*, **a**) to the intralaminar nuclei of the thalami (*arrows*, axial T2, **b**), the hypothalamus (*arrows*, axial T2, **c**) and the cerebral cortex generally (sagittal MPRAGE, **d**). The more inferior norepiephric centre in the dorsolateral medulla (*green circles*, graphic and axial T2, **f**) send neurons to the cerebellum (**g**, sagittal MPRAGE) and spinal cord (sagittal T2, **h**)

(BA 7) and the anterior insula cortex (involved in pain perception) when subjects changed the degree of attention they gave painful stimuli.

Mood-related changes in pain perception appear to act via a separate pathway. Activity in the lateral orbitofrontal cortex (BA 47) is associated with negative mood states, whereas activity in the medial orbitofrontal cortex (BA 45) is associated with positive mood states (Fig. 51) [24, 25].

Both these regions have extensive connections with other parts of the brain involved in sensory, and also pain processing; particularly the amygdala and periaqueductal grey matter (PAG). They are also connected to the anterior cingulum, a region of the brain associated with detecting the affective, or 'mood'-related component to a painful stimulus. It would appear that a negative mood (associated with increased activity in the lateral orbitofrontal cortex) may increase pain perception via facilitation of pain-related thalamocortical pathways, including the anterior cingulum, but also through reduction in inhibitory activity mediated at the dorsal horn level from the PAG and raphe nucleus.

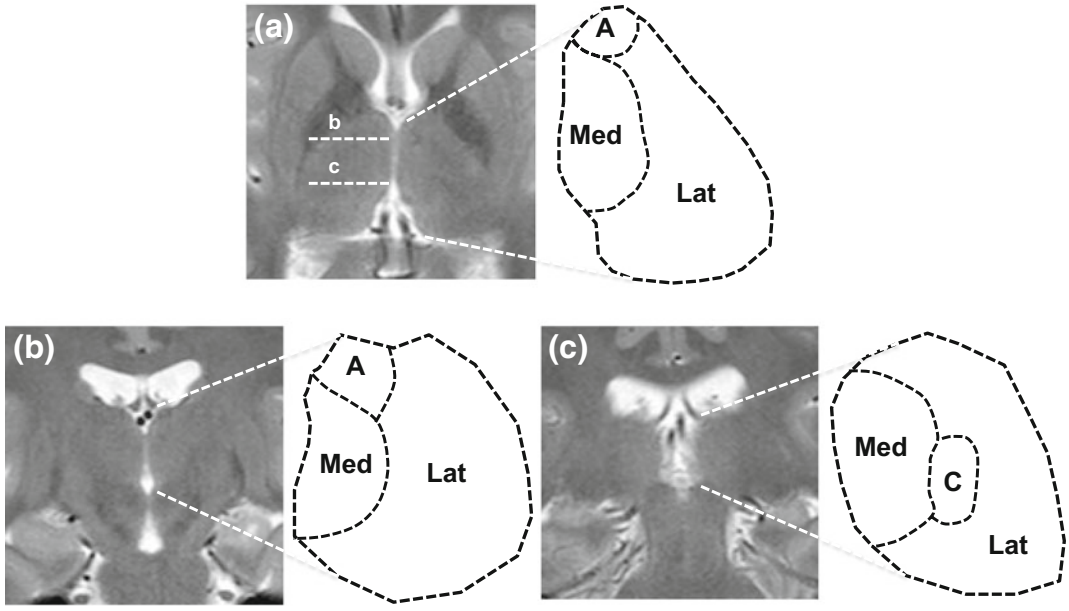

Fig. 43 The broad grouping of thalamic nuclei is shown on axial T2 image (**a**) with schematic; coronal sections at approximate locations (**b**) and **c** show the relative arrangement of the nuclear groups, including the intralaminar nuclei (**c**). *A* Anterior group, *Med* medial group, *lat* lateral group, *c* intralaminar nuclei

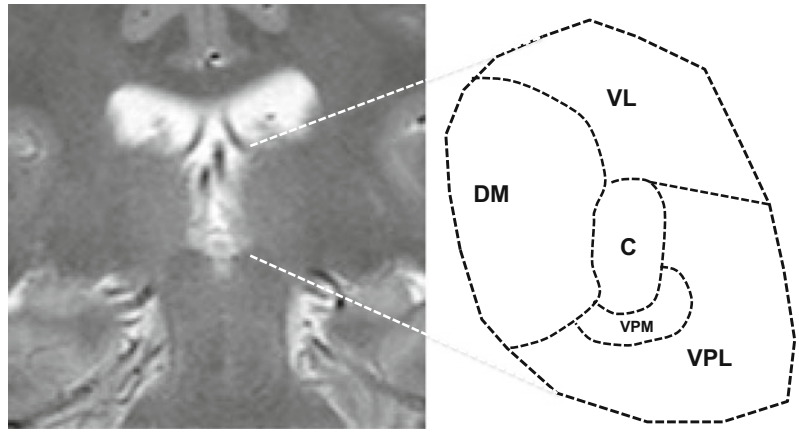

Fig. 44 Coronal T2 (*left*) and schematic showing the more detailed arrangement of the primary sensory nuclei within the ventrolateral thalamic group (the VPM and VPL). *DM* Dorsomedial, *VL* ventral lateral, *C* intralaminar, *VPM* ventroposteromedial, *VPL* ventroposterolateral

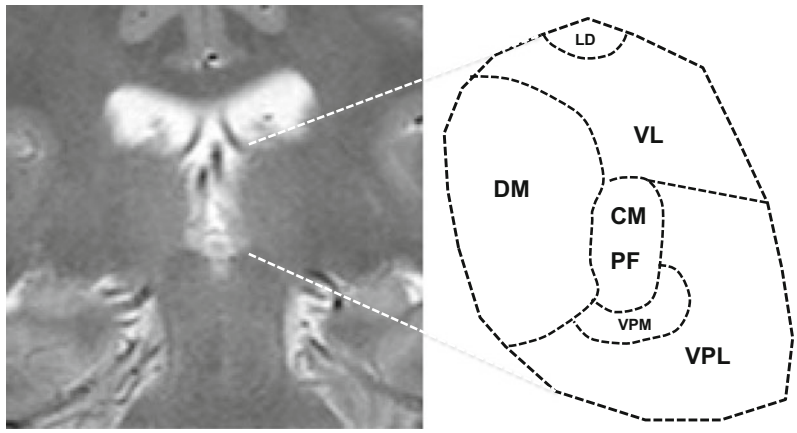

Fig. 45 Coronal T2 image and schematic showing subdivision of intralaminar nuclei—the centromedian and parafascicular nuclei. The laterodorsal nucleus is also shown on the superiormost surface of the thalamus. *LD* Laterodorsal, *DM* dorsomedial, *CM* centromedian, *PF* parafascicular, *VPM* ventroposteromedial, *VPL* ventroposterolateral

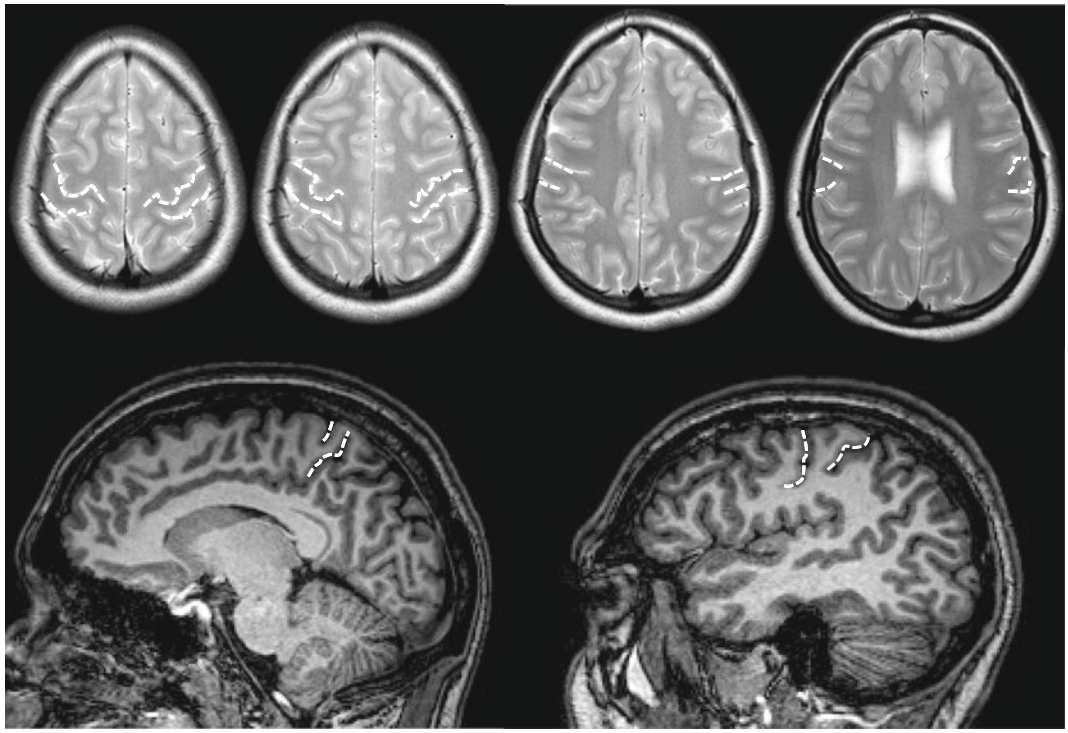

Fig. 46 Axial T2 (*top row*) and sagittal/parasagittal MPRAGE (*bottom row*) showing location of the primary sensory cortex (postcentral gyrus) between *dashed lines*

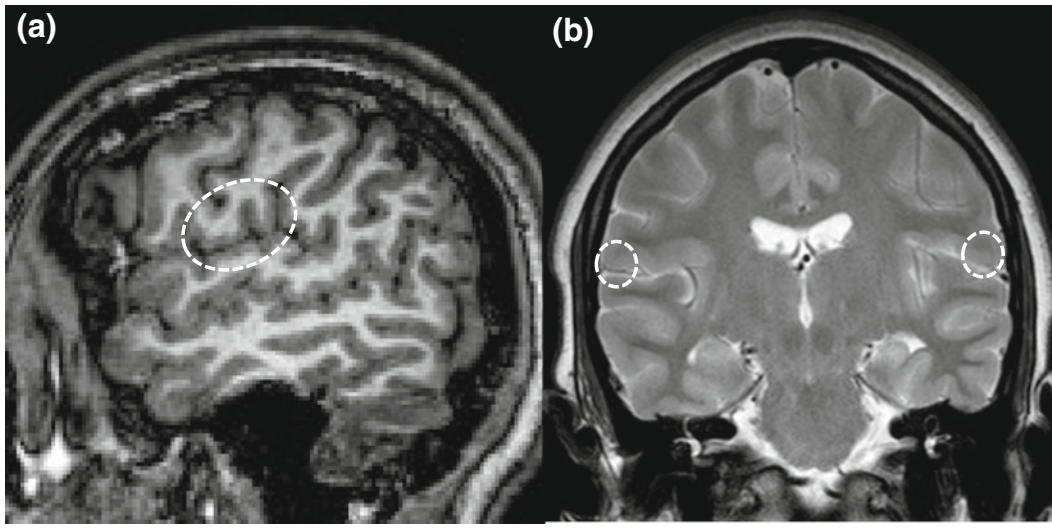

Fig. 47 Sagittal MPRAGE (**a**) and coronal T2 (**b**) showing the location of the secondary somatosensory cortex (*dashed circles*), spanning the sylvian fissure onto the superior temporal gyrus

14 Conclusion

Even the relatively basic neuroanatomy of sensory perception can appear complicated on first encounter with different brainstem tracts for different modalities of sensory perception, which move location at different levels. Add to this the extensive interconnectivity of the brainstem reticular system and the influence of widespread functional cortical networks and it can be easily seen that an appreciation of whole brain neuroanatomy is essential to understand this rapidly evolving field.

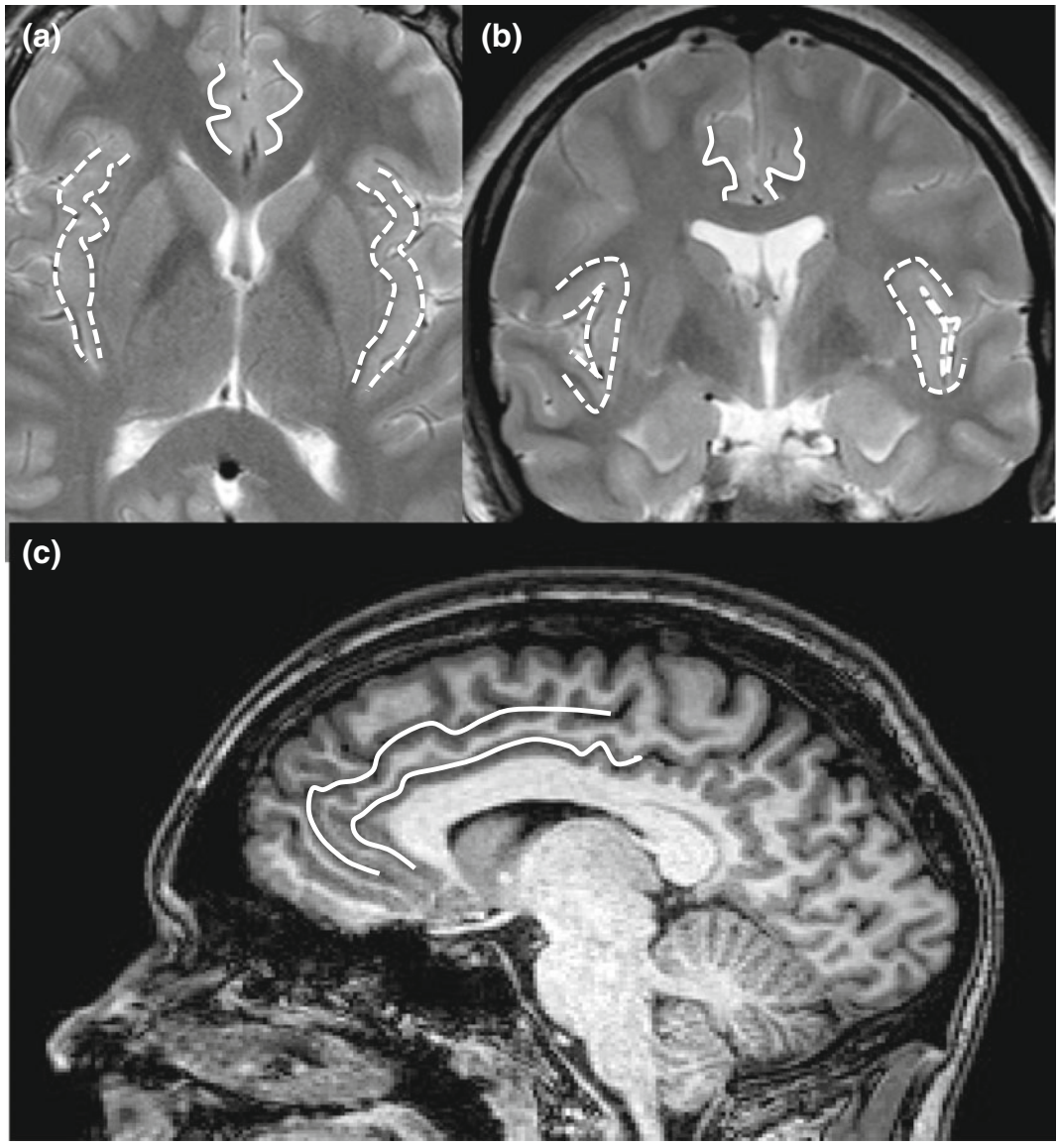

Fig. 48 Axial T2 (**a**), coronal T2 (**b**) and sagittal MPRAGE (**c**) showing the location of the insular cortex (between *dashed lines*) and anterior cingulate cortex (between *solid lines*)

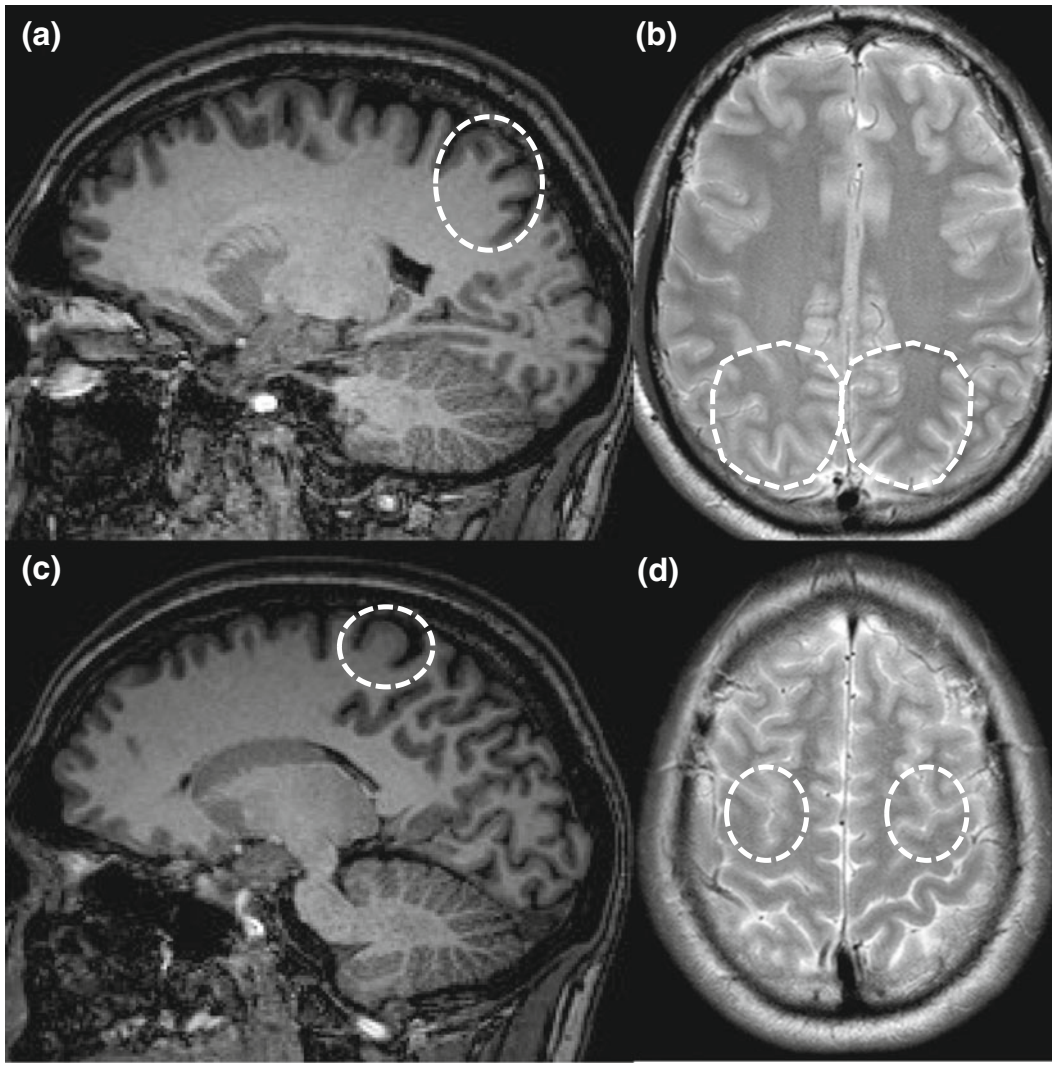

Fig. 49 Sagittal MPRAGE (**a**, **c**) and axial T2 (**b**, **d**) showing the location of Brodmann area 7 (**a**, **b**) and the frontal eye fields (**c**, **d**), *dashed circles*

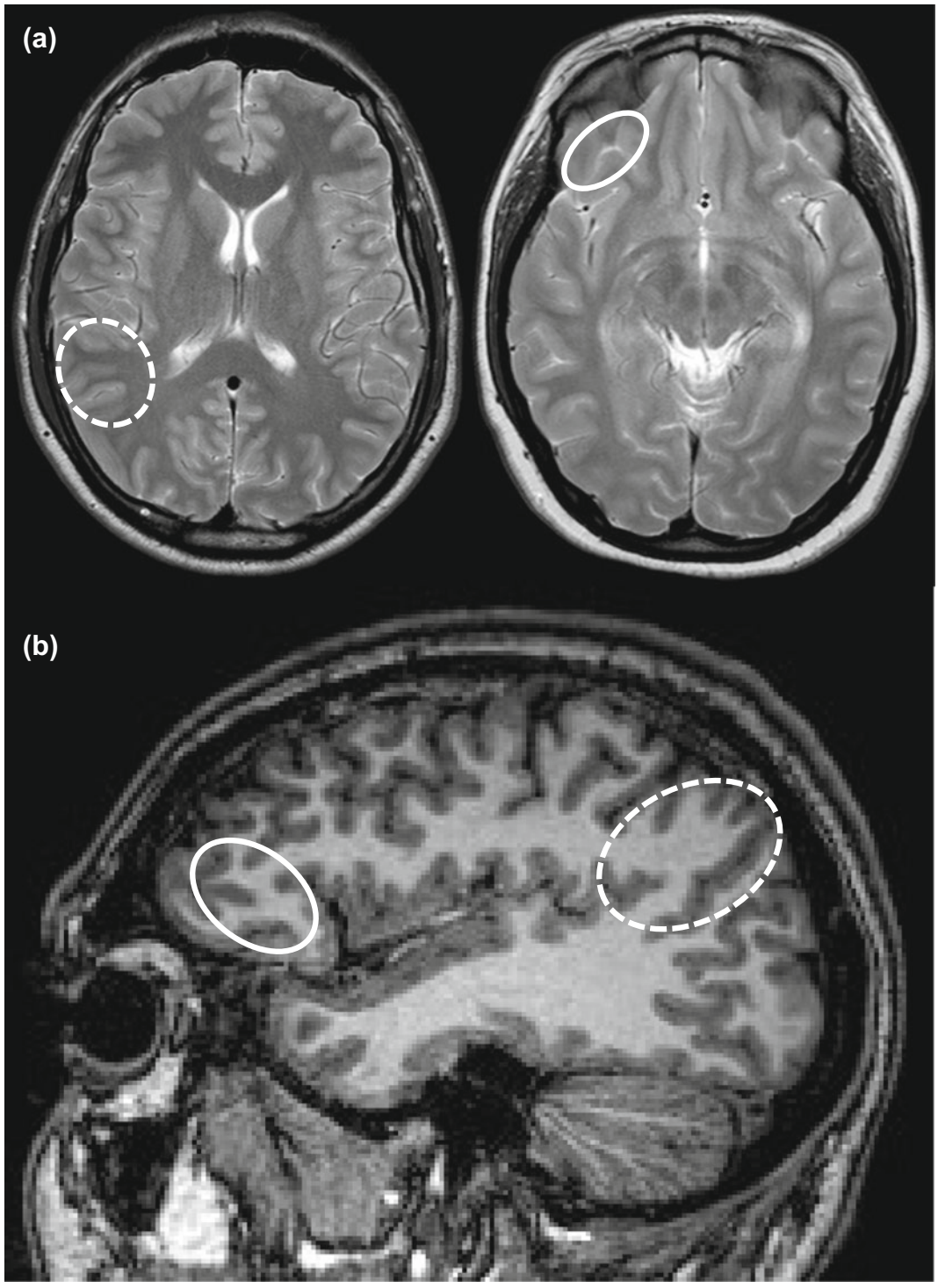

Fig. 50 Axial T2 (**a**) and parasagittal MPRAGE (**b**) showing the right-lateralised centres in the inferior parietal lobule (*dashed circle*) and inferior frontal gyrus (*solid circle*)

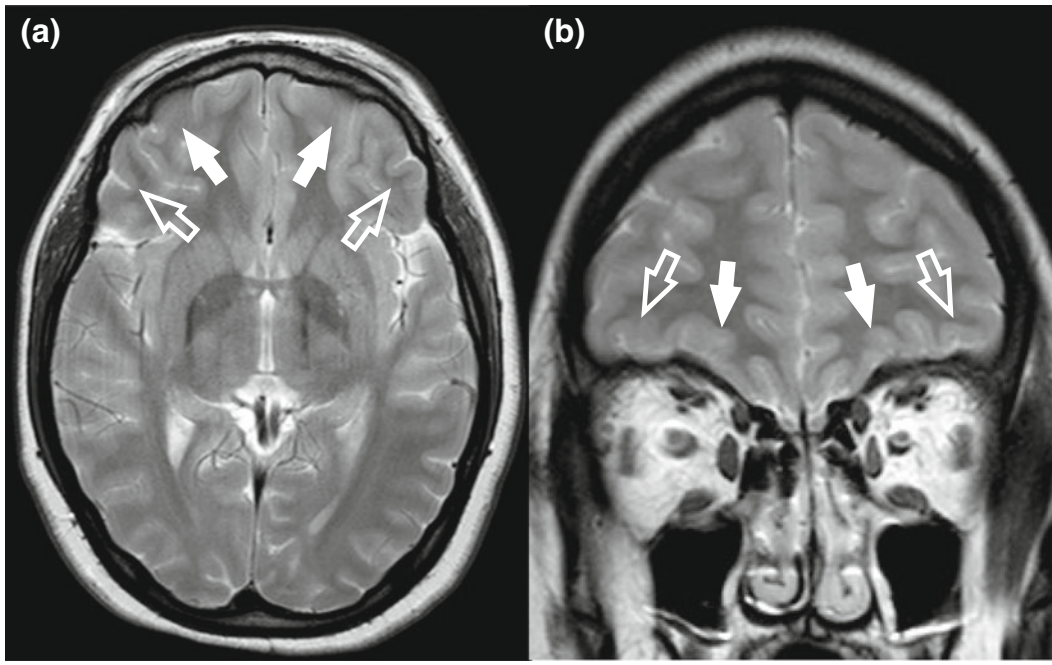

Fig. 51 Axial (**a**) and coronal (**b**) T2 images showing the location of the medial (*solid arrows*) and lateral (*open arrows*) orbitofrontal cortex

References

1. Schoewolf GC, Bleyl SB, Brauer PR, et al. Larsen's human embryology. 5th ed. London: Churchill Livingstone; 2014.
2. Nolte J. The human brain: an introduction to its functional anatomy. 6th ed. Missouri: Mosby; 2008.
3. Hathout GM. Clinical neuroradiology: a case-based approach. Cambridge: Cambridge University Press; 2008.
4. Thomas AG, Koumellis P, Dineen RA. The fornix in health and disease: an imaging review. Radiographics. 2011;31:1107–21.
5. Shah A, Jhawar SS, Goel A. Analysis of the anatomy of the Papez circuit and ajoining limbic system by fiber dissection techniques. J Clin Neurosci. 2012;19:289–98.
6. Whalen PJ, Phelps EJ, editors. The human amygdala. New York: Guilford Press; 2009.
7. Gerrish AC, Thomas AG, Dineen RA. Brain white matter tracts: functional anatomy and clinical relevance. Semin Ultrasound CT MR. 2014;35:432–44.
8. Hussain A, Utz MJ, Tian W, et al. Imaging and diseases of the ascending and descending pathways. Semin Ultrasound CT MR. 2014;35:474–86.
9. Barkovich AJ, Raybaud C. Pediatric neuroimaging. Philadelphia: Lippincott Williams and Wilkins; 2011.
10. Osborne AG. Diagnostic cerebral angiography. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 1999.
11. Patestas M, Gartner LP. A textbook of neuroanatomy. Hoboken: Wiley-Blackwell; 2006.
12. Kamali A, Kramer LA, Butler IJ, et al. Diffusion tensor tractography of the somatosensory system in the human brainstem: initial findings using high isotropic spatial resolution at 3.0T. Eur Radiol. 2009;19:1480–8.
13. Becker M, Kohler R, Vargas MI, et al. Pathology of the trigeminal nerve. Neuroimaging Clin N Am. 2008;18:283–307.
14. Sarrazin JL, Toulgoat F, Benoudiba F. The lower cranial nerves: IX, X, XI, XII. Diagn Interv Imaging. 2013;94:1051–62.
15. Neugebauer V. Amygdala pain mechanisms. Handb Exp Pharmacol. 2015;227:261–84.
16. Wilis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol. 1997;14:2–31.
17. Bender B, Mänz C, Korn A, et al. Optimized 3D magnetization-prepared rapid acquisition of gradient echo: identification of thalamus substructures at 3T. AJNR Am J Neuroradiol. 2011;32:2110–5.
18. Tourdias T, Saranathan M, Levesque IR, et al. Visualization of intra-thalamic nuclei with optimized white-matter-nulled MPRAGE at 7T. Neuroimage. 2013;84:534–45.
19. Omori S, Isose S, Otsuru N, et al. Somatotopic representation of pain in the primary somatosensory cortex (s1) in humans. Clin Neurophysiol. 2013;124:1422–30.

20. Chen TL, Babiloni C, Ferretti A, et al. Human secondary somatosensory cortex is involved in the processing of somatosensory rare stimuli: an fMRI study. NeuroImage. 2008;40:1765–71.
21. Mazzola L, Faillenot I, Barral F-G, et al. Spatial segregation of somato-sensory and pain activations in the human operculo-insular cortex. NeuroImage. 2012;60:409–18.
22. Plega B, Villringer A. The human somatosensory system: from perception to decision making. Prog Neurobiol. 2013;103:76–97.
23. Hayes DJ, Northoff G. Common brain activations for painful and non-painful aversive stimuli. BMC Neurosci. 2012;13:60.
24. Villemure C, Schweinhardt P. Supraspinal pain processing: distinct roles of emotion and attention. Neuroscientist. 2010;16:276–84.
25. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol. 2004;72:341–72.

Author Biography

Dr. Adam G. Thomas trained in medicine at University College London, graduating with honours. He obtained Membership of the Royal College of Physicians (UK) and Fellowship of the Royal College of Radiologists during postgraduate medical and radiology training and graduated with distinction from the Masters programme in Translational Neuroimaging at the University of Nottingham in 2012. He is a Consultant Neuroradiologist with expertise in paediatric neuroradiology at Nottingham University Hospitals, Queens Medical Centre, UK.