Stereotactic localization of the human pedunculopontine nucleus: atlas-based coordinates and validation of a magnetic resonance imaging protocol for direct localization

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The pedunculopontine nucleus (PPN) is a promising new target for deep brain stimulation (DBS) in parkinsonian patients with gait disturbance and postural instability refractory to other treatment modalities. This region of the brain is unfamiliar territory to most functional neurosurgeons. This paper reviews the anatomy of the human PPN and describes novel, clinically relevant methods for the atlas-based and MRI-based localization of the nucleus. These two methods of PPN localization are evaluated and compared on stereotactic MRI data acquired from a diverse group of 12 patients undergoing implantation of deep brain electrodes at sites other than the PPN. Atlas-based coordinates of the rostral and caudal PPN poles in relation to fourth ventricular landmarks were established by amalgamating information sourced from two published human brain atlases. These landmarks were identified on acquired T1 images and atlas-derived coordinates used to plot the predicted PPN location on all 24 sides. Images acquired using a specifically modified, proton-density MRI protocol were available for each patient and were spatially fused to the T1 images. This widely available and rapid protocol provided excellent definition between gray and white matter within the region of interest. Together with an understanding of the regional anatomy, direct localization of the PPN was possible on all 24 sides. The coordinates for each directly localized nucleus were measured in relation to third and fourth ventricular landmarks. The mean (SD) of the directly localized PPN midpoints was 6.4 mm (0.5) lateral, 3.5 mm (1.0) posterior and 11.4 mm (1.2) caudal to the posterior commissure in the anterior commissure–posterior commissure plane. For the directly localized nucleus, there was similar concordance for the rostral pole of the PPN in relation to third and fourth ventricular landmarks (P > 0.05). For the caudal PPN pole, fourth ventricular landmarks provided greater concordance with reference to the anteroposterior coordinate (P < 0.001). There was a significant difference between localization of the PPN poles as predicted by atlas-based coordinates and direct MRI localization. This difference affected mainly the rostrocaudal coordinates; the mean lateral and anteroposterior coordinates of the directly localized PPN poles were within 0.5 mm of the atlas-based predicted values. Our findings provide simple, rapid and precise methods that are of clinical relevance to the atlas-based and direct stereotactic localization of the human PPN. Direct MRI localization may allow greater individual accuracy than that afforded by atlas-based coordinates when localizing the human PPN and may be relevant to groups evaluating the clinical role of PPN DBS.

Keywords: pedunculopontine nucleus; stereotactic localization; deep brain stimulation
Introduction

In advanced Parkinson’s disease, gait disturbance and postural instability are often refractory to current treatment modalities. Deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) is a novel surgical approach with the potential of providing relief from these severely disabling symptoms (Jenkinson et al., 2005; Plaha and Gill, 2005).

The PPN is a functional component of the rostral locomotor region of the brainstem and is thought to play a central role in the initiation and maintenance of gait (Pahapill and Lozano, 2000). Evidence from animal experiments is compelling: electrical stimulation of the PPN in decerebrate animals induces controlled locomotion (Garcia-Rill et al., 1987), lesions of the PPN in normal primates result in akinesia (Kojima et al., 1997; Munro-Davies et al., 2001) and chemical disinhibition of the PPN using microinjections of the GABA antagonist bicuculline has been observed to alleviate akinesia in the parkinsonian primate (Nandi et al., 2002). Finally, PPN stimulation was effective in improving akinesia in a parkinsonian monkey (Jenkinson et al., 2004). Two pioneering groups have reported their preliminary experience in targeting the region of the PPN in humans: they observed a significant improvement in gait dysfunction and postural instability with low-frequency stimulation (20–25 Hz) in both the ‘on’ and ‘off’ medication states (Mazzone et al., 2005; Plaha and Gill, 2005; Stefani et al., 2007).

The PPN is an elongated neuronal collection in the lateral pontine and mesencephalic tegmental zones (Fig. 1A and B). With its long axis roughly parallel to the long axis of the floor of the fourth ventricle, the nucleus straddles the pontomesencephalic junction (Nieuwenhuys et al., 1988) extending circa 5 mm from the mid-inferior collicular level to reach the rostral pons (Olszewski and Baxter, 1982; Paxinos and Huang, 1995). A noteworthy feature is the triad of projection-pathways that circumscribes the region of the PPN: the superior cerebellar peduncle and its decussation, the central tegmental tract and the curved band of the lemniscal system. In the pontine tegmentum, the PPN lies in the gray matter at the elbow formed laterally by the lemniscal system and medially by the superior cerebellar peduncle. In the mesencephalic tegmentum, the nucleus lies dorsolateral to the decussation of the superior cerebellar peduncles, hugging the lateral border of the central tegmental tract and still bounded laterally by the lemniscal tracts. This region of the brain is unfamiliar territory to most functional neurosurgeons and targeting errors may result if the anatomy of the region is not well understood (Zrinzo et al., 2007a, b; Yelnik, 2007).

Atlas-based stereotactic coordinates of the PPN in relation to ventricular landmarks are not well established. The Schaltenbrand and Wahren stereotactic atlas (Schaltenbrand and Wahren, 1977), a popular reference amongst functional neurosurgeons, identifies the PPN (nucleus tegmenti pedunculopontinus – Tg.pdpo) but does not provide a clear demarcation of its borders (Fig. 2). This is a consequence of the histological basis of the atlas and the reticular nature of the nucleus (Olszewski and Baxter, 1982). We reviewed a number of other human brain atlases in order to determine the most accurate set of atlas-based coordinates for the PPN (Afshar et al., 1978; Olszewski and Baxter, 1982; Talairach and Tournoux, 1988; Paxinos and Huang, 1995). Taken alone, none of these atlases define the boundaries of the PPN within stereotactic space. However, direct comparison between the atlas of Paxinos and Huang and that of Afshar, Watkins and Yap is possible since they present axial sections taken at 1 mm intervals in a plane perpendicular to the long axis of the medulla and pons and to the midline of the fourth ventricular floor (VFL), respectively. Photographs and corresponding labelled contour drawings are included in both publications (Fig. 1A–D).

The histochemically based Paxinos atlas currently provides the most comprehensive delineation of the boundaries of the human PPN (Fig. 1A and B) (Paxinos and Huang, 1995). Based on one human cadaveric brainstem, this atlas does not incorporate a stereotactic localization system. In contrast, Afshar’s stereotactic atlas is compiled from information acquired from 30 human cadaveric hemi-brainstems (Afshar et al., 1978). Dedicated to stereotactic localization of structures within the brainstem, it presents quantitative data based on variability between individuals. This atlas adopts a stereotactic reference system based upon fourth ventricular landmarks rather than the more traditional landmarks related to the third ventricle (Fig. 3).

We hypothesized that the integrated information sourced from the two atlases (Fig. 1A–D), would allow a probabilistic assessment of PPN location within a stereotactically defined space thus providing atlas-based coordinates for the PPN (Fig. 1).

Coordinates derived from stereotactic atlases minimize, but do not abolish, targeting errors secondary to anatomical variation. By allowing direct visualization of certain anatomical structures, high resolution, high definition, stereotactic MRI eliminates the problem of anatomical variability (Vayssiere et al., 2002; Ashkan et al., 2007). The merits of this approach have gained it increasing acceptance in functional neurosurgery and have led to the publication of clinically applicable MRI protocols designed...
Fig. 1 Axial sections perpendicular to long axis of brainstem. Row I: level of rostral PPN and mid inferior colliculi (IA and IB: 36 mm rostral to obex; IC and ID: 16 mm rostral to BF plane). Row II: through middle of PPN (IIA and IIB: 33 mm rostral to obex; IIC and IID: 13 mm rostral to BF plane). Row III: sections taken through caudal PPN (IIIA and IIIB: 31 mm rostral to obex; IIIC and IIID: 11 mm rostral to BF plane). Columns A and B: adapted from Paxinos et al. Column A presents negative photographs of sections stained with cresyl violet and acetylcholinesterase: white matter appears dark, gray matter appears light. Line drawings presented in column B show the outline of fibre
for the visualization of specific targets such as the subthalamic nucleus and pallidum (Bejani et al., 2000; Hirabayashi et al., 2002; Hariz et al., 2003). Specific MRI parameters for the direct localization of the human PPN in vivo have not been previously detailed. Direct MRI localization may improve the accuracy and reliability of surgical targeting of the PPN in patients undergoing DBS.

Here we describe a method for direct MRI localization of the PPN in a series of patients. Using this localization method we then evaluate the location of the human PPN in relation to third and fourth ventricular landmarks and compare our findings to PPN localization based upon published atlases.

Methods
In view of the orientation of the nucleus in line with the long axis of the brainstem, we elected to characterize the coordinates of its rostral and caudal poles.

Fourth ventricular landmarks and atlas-based coordinates
The location and configuration of the PPN were defined by integrating information from two atlases (Figs 1A–D) (Afshar et al., 1978; Paxinos and Huang, 1995). The Paxinos atlas demonstrates the PPN and its relations to the surrounding projection-pathways—the lemniscal system, central tegmental tract and decussating superior cerebellar peduncles. The rostral pole of the nucleus can be identified at mid-inferior collicular level; the caudal pole lies in the rostral pons with the nucleus spanning a distance of 5 mm (Fig. 1A and B) (Paxinos and Huang, 1995).

Although Afshar’s atlas does not label the PPN, the locations of the surrounding fibre-systems are defined in stereotactic space. These anatomical relations allow a probabilistic assessment of the atlas-based coordinates of the two poles of the PPN in the corresponding axial sections at mid-inferior collicular level and 5 mm caudally (Fig. 1C and D). Afshar’s stereotactic atlas adopts a reference system based upon fourth ventricular landmarks: the fastigial point (F), a line tangential to the floor of the fourth ventricle, and another perpendicular to the first and passing through the fastigium; the intersection determines the base point (B) (Fig. 3). The axial plane is defined as passing perpendicular to VFL.

Protocols used for direct MRI localization of the PPN
We reviewed preoperative stereotactic MR images of patients who had previously undergone implantation of DBS electrodes in other anatomical targets to assess whether imaging protocols that are already in current use would be valuable in defining PPN localization in vivo. Appropriate stereotactic MR images from a diverse group of 12 consecutive patients were analysed (mean age 42 years, range 16–69; male: 5; indications: Parkinson’s disease 4, Dystonia 8). The Leksell Coordinate Frame® (Model G; Elekta Instrument AB, Stockholm, Sweden) had been applied to the head with base ring parallel to Reid’s base line (Reid, 1884). The frame was oriented orthogonally with the scanner bore, minimizing skew and optimizing congruency in the axes of head, frame and scanning planes.

T1-weighted and proton density stereotactic MR images from the region of the anterior and posterior commissures (AC and PC) to the lowerpons were available in all 12 patients (1.5T Signa MRI scanner: General Electric, Milwaukee, WI). T1-weighted imaging was obtained using a volumetric axial SPGR sequence orthogonal to the stereotactic frame (slice thickness 2 mm; FA 30°; 1 echo; BW 15.63; FOV 250 mm; matrix 256 x 256; acquisition time ~5 min 20 s). Proton density images were obtained in the axial plane and orthogonal to the stereotactic frame (slice thickness 2 mm contiguous; TR/TE 4000/15; echo-train 7; NEX 3; BW 15.63; FOV 250 mm; matrix 256 x 256; acquisition time ~7 min).

Using commercially available planning software (FrameLink™; Medtronic, Minneapolis, MN, USA) the datasets from the two imaging sequences of each patient were spatially fused; the facility for the sequences to be viewed independently was retained. Despite an acquisition voxel size of 1.0 x 1.0 x 2.0 mm³, software interpolation allowed image viewing in 1 mm steps in all three planes. Relevant anatomical landmarks were identified and marked on the reconstructed axial and sagittal T1 images: the AC and PC, F, VFL and B (Fig. 3).

The fused datasets of each patient were reformatted to render axial images parallel to the B–F plane. This manoeuvre allowed the
direct comparison between the reformatted MRI images and the Paxinos and Afshar atlases. On the mid-sagittal image, we extrapolated the AC–PC line and the VFL and termed the enclosed sagittal angle ‘the mesencephalic angle’ (Fig. 3). The mesencephalic angle was determined for each patient after importing midline sagittal images into image manipulation software (Adobe Photoshop Elements 4.0: Adobe Systems Incorporated, San Jose, CA, USA).

Using the defined fourth ventricular landmarks and measurements derived from the Afshar atlas, the atlas-derived coordinates for the rostral and caudal poles of the PPN were transferred onto the T1-weighted image dataset of each patient. The PPN was thereby indirectly localized on all 24 sides of the T1 axial sections without any cross-reference to the proton density images.

By browsing through the reformatted axial and sagittal T1 images, the mid-inferior collicular level could be determined (Fig. 4A); the axial slice demonstrating the maximal basal diameter of the inferior colliculus was appraised as that at mid collicular level and containing the rostral PPN pole. The distance between the axial section at this level and the B–F plane was recorded for each patient. Although this allowed the rostrocaudal span of the PPN to be inferred, the T1 images did not provide sufficient gray/white matter differentiation to allow recognition of anatomical structures within the pontomesencephalic axial sections (Fig. 4A). On the other hand, the axial proton density images of the region provided excellent MR correlates of the internal architecture presented on atlas sections (Fig. 4B) allowing for direct localization of the PPN. The coordinates of the directly localized PPN poles in relation to fourth ventricular landmarks were recorded.

The fused datasets of each patient were then reformatted to render axial images according to the AC–PC plane. This manoeuvre allowed calculation of the coordinates of the directly localized PPN poles in relation to the AC–PC landmarks.

Statistics
The one-sample t-test was used to identify significant differences between direct PPN localization and the location predicted by atlas-derived coordinates. The F-test for variance was used to examine whether the directly localized PPN showed significantly greater concordance with third or fourth ventricular landmarks. The level of significance was chosen at $P < 0.05$.

Results

Atlas-based coordinates and landmarks
Our review of atlases incorporating the brainstem provided a means of PPN localization with reference to fourth ventricular landmarks. By amalgamating information from the atlas of Paxinos with that of Afshar, atlas-based coordinates for the rostral pole of the PPN were defined as 6 mm lateral and 4 mm anterior to the base point (B), 16 mm rostral to the base point–fastigial (B–F) plane; those for the caudal pole were 7 mm lateral and 4 mm anterior to B, 11 mm rostral to the B–F plane (Fig. 4A).

The variability in the mesencephalic angle, a factor necessarily influencing the spatial inter-relations between third and fourth ventricular landmarks, was also ascertained. The mean mesencephalic angle in our series of 12 patients was $104^\circ$ (SD 2°; range 100–107°) (Fig. 3).
could be demarcated bounded anterolaterally by the ML, anteromedially by the DSCP and posteromedially by the CTT. The rostral PPN lies within this region adjacent to the lateral border of the CTT. The mean (SD) coordinates of the MRI-localized rostral pole were 6.0 mm (0.5) lateral and 4.2 mm (0.8) anterior to B, 19.3 mm (1.4) rostral to the B–F plane. Individual data are presented in Table 1.

On the more caudal proton density axial images, the lemniscal system and the superior cerebellar peduncle could be traced to a region where the gray matter between these fibre tracts is compressed to a narrow boomerang shape (Fig. 1.II and 1.III). In the axial section 5 mm caudal to the mid-inferior collicular level, the caudal pole of the PPN occupies the slender region of the genu of this gray matter. It could be recognized, albeit with some difficulty, as the area of intermediate signal intensity tightly packed between the hypointensities of the superior cerebellar peduncle medially and the lemniscal system laterally (Fig. 1.III). The mean (SD) coordinates of the MRI-localized caudal pole were 6.8 mm (0.5) lateral and 4.4 mm (0.5) anterior to B, 14.3 mm (1.4) rostral to the B–F plane. Individual data are presented in Table 1.

With images reformatted in relation to third ventricular landmarks, the coordinates of the MRI-localized PPN poles were determined in relation to the posterior commissure (PC); individual results are presented in Table 2. The mean (SD) coordinates for the rostral pole were 6.0 mm (0.5) lateral and 3.0 mm (1.1) posterior to the PC, 9.0 mm (1.1) caudal to the AC–PC plane; those of the MRI-localized caudal pole were 6.8 mm (0.5) lateral and 4.0 mm (1.1) posterior to the PC, 13.9 mm (1.2) caudal to the AC–PC plane. We also determined the coordinates of the PPN midpoint with respect to the PC and the AC–PC plane: 6.4 mm (0.5) lateral, 3.5 mm (1.0) posterior and 11.4 mm (1.2) caudal to the posterior commissure.

**Comparison of atlas-based coordinates and MRI-based coordinates**

We compared the predicted location of the atlas-derived PPN coordinates with the observed individual coordinates of the MRI-localized nucleus in relation to fourth ventricular landmarks. Using the one-sample t-test, we found no significant difference in the lateral and anteroposterior coordinates of the rostral pole ($P > 0.05$). However, there was a highly significant difference between the predicted and observed rostrocaudal coordinate of the rostral pole (mean 16.0 mm versus 19.3 mm; $P < 0.001$). For the caudal pole there was a statistically significant difference between predicted and observed values for all three coordinates (lateral: 7.0 mm versus mean 6.8 mm, $P < 0.05$; anteroposterior: 4.0 mm versus mean 4.4 mm, $P < 0.05$; rostrocaudal: 11.0 mm versus mean 14.3 mm, $P < 0.001$).

**MRI localization and MRI-based coordinates**

We determined that a previously published imaging protocol designed to visualize the laminae and subdivisions of the globus pallidus reliably provides excellent gray/white matter differentiation in the rostral brainstem (Hirabayashi et al., 2002). Combined with knowledge of local anatomy, in particular the relation of the nucleus to its three neighbouring fibre-systems, this protocol provides a rapid and precise acquisition of the MRI-based coordinates of the human PPN (Fig. 1E and F).

MRI-based localization of the rostral PPN was easily performed on all 24 sides (Figs. 1E, F and 4B). On axial proton density images reformatted in relation to fourth ventricular landmarks, white matter tracts at mid-inferior collicular level were seen to form a distinctive hypointense pattern: the decussation of the superior cerebellar peduncles (DSCP) could be easily visualized in the ventral tegmentum with the medial lemniscus (ML) coursing posterolaterally from its anterolateral aspect. The central tegmental tracts (CTT) could be identified abutting the ventral aspect of the hyperintense periaqueductal gray (PAG). A region of intermediate signal intensity denoting reticular gray matter

Fig. 3 Atlas-based landmarks of the fourth ventricle as defined in Afshar’s stereotactic atlas of the human brainstem and cerebellum. Variability in the angle of the mesencephalic flexure (a) may lead to increased variability of the spatial relationship of brainstem structures to the traditional AC-PC line. Brainstem structures may therefore enjoy a more constant relationship with fourth ventricular landmarks. A line is drawn tangential to the floor of the fourth ventricle in the midline (VFL); a second line passes through the fastigium, perpendicular to the first. The intersection of these two lines (B) and the fastigial point (F) define two points in a new reference plane in a similar manner to that defined by the more traditional AC-PC points. Extensions of the VFL and the AC-PC line subtext an angle a: the mesencephalic angle.
Relations between anatomical landmarks and MRI-localized PPN

In our series of patients, the MRI-localized PPN midpoint was equidistant from the mid B–F and mid AC–PC points (mean distance of 20 mm from both landmarks). We compared the observed variance in the relation of the MRI-localized PPN to B to that in relation to PC. Using the F-test, we found no significant difference for any of the three coordinates of the rostral pole (\(P > 0.05\)). For the caudal pole, there was no significant difference between the observed variance in the lateral and rostrocaudal coordinates as measured from B and PC (\(P > 0.05\)). However, variance in the anteroposterior coordinate of the caudal pole was significantly higher in relation to PC than in relation to B (1.2 mm versus 0.3 mm, \(P < 0.001\)).

Discussion

This paper offers a detailed description of the anatomical relations of the human PPN, in particular to the fibre-systems circumscribing the nucleus. It presents a specific MRI protocol that allows localization of the PPN in patients. It also characterizes, for the first time, the atlas-based coordinates of the nucleus with reference to fourth ventricular landmarks.

The elongated orientation of the PPN within the brainstem is of practical importance and has implications on the trajectory of an implanted DBS electrode when attempting placement of as many contacts as possible within the nucleus. Additionally, anatomical localization of a reticular nucleus cannot rely on identification of the structural borders since, by definition, these are ill-defined.
We therefore addressed these issues by localizing both rostral and caudal poles of the PPN rather than just the midpoint.

**Atlas-based coordinates versus mean of MRI-localized coordinates**

We examined whether predicted PPN location, based upon atlas-derived coordinates in relation to fourth ventricular landmarks, agreed with the observed MRI-localization. For both rostral and caudal poles, we noted a significant difference between the predicted and observed rostrocaudal coordinate in relation to the B point (16.0 mm versus mean 19.3 mm and 11.0 mm versus mean 14.3 mm, respectively; \( P < 0.001 \)). This discrepancy of 3.3 mm may be clinically relevant when considering surgical targeting of the PPN. This finding could be explained by a more caudal location of the fastigium in our patient series relative to that portrayed in Afshar’s atlas. Indeed, a study comparing imaging findings of the brainstem to Afshar’s atlas makes the observation that the MR visualized fastigium was often displaced in a more caudal location than that predicted by the atlas (Niemann et al., 1999). These findings cast some doubt on the suitability of the B–F line as an appropriate landmark for stereotactic localization. Nonetheless, this variability can be circumvented by defining axial planes orthogonal to the extrapolated length of the VFL other than the B–F plane. Another possible explanation for this discrepancy could be that the voxel size used (1 mm × 1 mm × 2 mm) may lead to reduced accuracy of localization in the rostrocaudal dimension when compared to the axial plane. Based on information from the Paxinos atlas, the axial plane at mid-inferior collicular level establishes the rostrocaudal coordinate of the rostral PPN pole; knowledge that the nucleus spans a distance of 5 mm along the long axis of the brainstem establishes the respective location of the caudal pole (Paxinos and Huang, 1995).

For lateral and anteroposterior coordinates of the rostral pole, there was no significant difference between atlas-derived calculations and measurements based on the
MRI-localized nucleus. For the caudal pole, the difference between atlas-derived calculations and the MRI-localized values for lateral and anteroposterior coordinates was statistically significant. However the magnitude of this difference (lateral: 7.0 mm versus mean 6.8 mm; anteroposterior: 4.0 mm versus mean 4.4 mm) suggests that these differences may not be clinically relevant.

Despite the lack of well-defined PPN borders, the Schaltenbrand atlas corroborates our assessment of the atlas-based coordinates of the PPN in relation to the AC–PC line (Fig. 2) (Schaltenbrand and Wahren, 1977). In Plate 29, which includes coronal views at 15.5 and 16.5 mm posterior to the midscomissural point, the PPN is labelled Tg.pdp; the coordinates for this structure are around 6–8 mm lateral, 3.5–4.5 mm posterior and 12–14 mm caudal to the PC. Values for our set of coordinates for the PPN midpoint obtained by measurement based on MRI acquired data were 6.4 mm (range 5.4–7.2 mm) lateral, 3.5 mm (range 1.6–5.5 mm) posterior and 11.4 mm (range 9.9–13.3 mm) caudal to the posterior commissure. These two sets of atlas-based coordinates are quite similar. However, they differ markedly from the set employed by other authors who have already attempted PPN DBS in the clinical setting: 9–13 mm lateral, 0 mm anteroposterior and 12.5/13 mm caudal to the posterior commissure (Stefani et al., 2007; Zrinzo et al., 2007b).

**Importance of anatomical targeting in functional neurosurgery**

Physiological methods, including microelectrode recording, local field potentials and clinical examination, are often used to refine localization during functional procedures. Teams differ in their approach to physiological assessment and the expected physiological signature of the PPN is as yet undefined. However, the universal first step of any functional neurosurgical procedure is anatomical targeting. Increased accuracy of anatomical targeting may allow acquisition of the desired target with the minimal number of passes through the brain. Postoperative stereotactic images documenting the anatomical intervention would then allow the acquired physiological data to be accurately linked to the targeted area.

**Concordance with ventricular landmarks**

Atlas-based localization of anatomical brain targets is a method widely used by functional neurosurgeons. Theoretically, greater proximity of landmarks to the target structure has a positive impact on the precise determination of their spatial relations. Most structures clinically relevant to functional neurosurgeons lie close to the third ventricle. The ease of identification of the anterior and posterior commissures on ventriculography and their proximity to these structures established the AC–PC line as the traditional stereotactic landmark. Fourth ventricular landmarks may be expected to be more appropriate when indirectly targeting brainstem structures. Afshar et al. (1978) recognized this concept and, in their stereotactic atlas of the human brainstem, they abandoned the traditional AC–PC landmarks in favour of the B–F plane (Fig. 2). However, the advantage of proximity of stereotactic landmarks may have been overshadowed by their potential variability, as later reported by Niemann et al. (1999).

We therefore explored whether the MRI-localized PPN holds a more constant relation with the B–F or AC–PC landmarks in our series of patients. Intriguingly, the mean location of the MRI-localized PPN midpoint was equidistant from the midpoint of both sets of ventricular landmarks (20 mm). Our observations determined that, for the majority of coordinates, there was no significant difference between the variance of the MRI-localized PPN poles in relation to B when compared to those same coordinates in relation to PC (F-test: $P > 0.05$). The exception was for the anteroposterior coordinate of the caudal PPN pole where there was significantly greater variance in relation to PC than to B (F-test: $P < 0.001$).

In mid-sagittal section, the long axes of the rhombencephalon and diencephalon lie at an angle to each other, a legacy of one of the main embryological cephalic folds, the mesencephalic flexure (Larsen, 1997). In our series of 12 adults, the mean mesencephalic angle was 104°, SD 2°, range 100°–107° (Fig. 2), a remarkably similar result to the 100° angle subtended at the mesencephalic flexure on day 23 after conception (Larsen, 1997). In relation to PC and the AC–PC plane, variation in the mesencephalic angle mainly impacts upon the anteroposterior coordinate of structures in the brainstem such as the PPN. This effect would be amplified with increasing rostrocaudal distance from the PC and may explain the greater observed variance of the anteroposterior coordinate in relation to PC affecting the caudal but not the rostral PPN pole.

Overall, these findings would suggest that either set of mean coordinates in relation to the two ventricular landmarks are of value in the atlas-based localization of the rostral PPN pole. Indeed, despite the known variability of the fastigial point, the mean value of coordinates in relation to fourth ventricular landmarks may be more reliable for predicting localization of the caudal PPN pole.

We observed considerable individual variation in PPN location in relation to both third and fourth ventricular landmarks (Tables 1 and 2). Reliance on atlas-based localization of the PPN might therefore be expected to lead to anatomical targeting errors in a number of patients. Nevertheless, the atlas-based coordinates defined earlier are useful in providing an estimate of PPN localization that can be further refined by MRI-localization using the described protocol. Local field potentials and microelectrode recording signatures of the human PPN are as yet undefined. Future studies could utilize this imaging method to confirm anatomical placement within the PPN and validate physiological recordings as being from this location.
MRI-based localization of the PPN

MRI sequences designed for the visualization of specific targets allow direct localization eliminating the problem of anatomical variability (Bejani et al., 2000; Hirabayashi et al., 2002; Vayssiere et al., 2002; Hariz et al., 2003). Groups utilizing MRI-directed targeting should be aware that MRI distortion may affect targeting accuracy. However, strict quality assurance of the equipment being used and described correction methods can reduce this to submillimetric levels (Menuel et al., 2005). The present study describes a modified proton density stereotactic MR protocol that reliably provides high contrast between gray and white matter in the pontomesencephalic region. The short acquisition time (~7 min) would allow the necessary imaging to be obtained without general anesthesia. The PPN could be directly localized as a region of intermediate signal intensity when compared to the hyperintensity of the periaqueductal gray (PAG) and the hypointensity of the neighbouring triad of white matter tracts (Fig. 4b). The MRI appearance of the PPN is, most probably, a reflection of the loose structure of the nucleus as a component of the lateral column of the reticular formation.

The mean lateral and anteroposterior coordinates of the directly localized PPN poles in relation to the midline of the fourth VFL were very similar to the atlas-based coordinates arrived at by the amalgamation of the atlases by Paxinos and Afshar. This concordance, as well as agreement with all three coordinates of the PPN midpoint derived from the Schaltenbrand and Wahren Atlas, provides a measure of inter-methodological validity between the accuracy of the atlases and that of the imaging technique.

Neuronal degeneration has been reported within the PPN in Parkinson’s disease (Hirsch et al., 1987; Jellinger, 1988; Zweig et al., 1989; Gai et al., 1991). This may give rise to concerns that imaging may not adequately visualize the PPN in parkinsonian patients who are being considered for DBS. In the four patients in this study who had advanced PD severe enough to warrant DBS in more traditional targets, the rostral pole of the PPN could be identified with ease; the caudal pole could also be recognized, albeit with some difficulty. Indeed, one of the advantages of this localizing method is that it is based on the identification of fibre-systems circumnscibing the nucleus and which are not known to be affected in Parkinson’s disease.

Conclusion

Reliable and accurate anatomical localization is an important factor when assessing the efficacy of the PPN as a potential target for DBS treatment in PD. This paper presents a proton density MRI protocol that, together with knowledge of local anatomy, allows rapid and accurate direct localization of the PPN. We describe the observed location of the rostral and caudal PPN poles in relation to third and fourth ventricular landmarks. This localization method is compared to that extrapolated from published human brain atlases. Our findings provide simple and rapid yet precise methods that are of clinical relevance to the atlas-based and MRI-based stereotactic localization of the human PPN. MRI localization may allow greater individual accuracy than that afforded by atlas-based coordinates when localizing the human PPN and may be relevant to groups evaluating the clinical role of PPN DBS.

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