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RAPID REPORT

THE HUMAN DENTATE NUCLEUS: A COMPLEX SHAPE UNTANGLED

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Abstract—The dentate nucleus is the largest single structure linking the cerebellum to the rest of the brain. The peculiar shape and large size of the human dentate nucleus have sparked a number of theories about the role of the cerebellum in human evolution. Some of the proposed ideas could be explored by comparative studies of humans and apes, but comparative studies are hindered because of the complex three dimensional shape of the human dentate. Here we present a 3D model based on a quantitative reconstruction of the human dentate; this model can facilitate comparative studies. The dentate nucleus has been partitioned into dorsal and ventral lamellae based on sheet thickness. Our data show that the thicker ventral lamella occupies a distinctly smaller portion of the human dentate than previously hypothesized. Within the dorsal lamella there is a medial to lateral increase in depth of dentate folds. However, the dorsal lamella retains a thin sheet thickness unlike the macrogyric ventral lamella, in which sheet thickness is increased. The appearance of larger folds laterally reflects the emergence of secondary folds that could encompass the projection of the cerebellar hemispheres, minimizing convergence of different corticonuclear microzones. Thus, the unique feature of the hominoid dentate is the development of a large surface area and an expansion of its mediolateral width. We propose that this is to allow for a large number of independent corticonuclear modules that can modulate an equal large number of sequential motor acts. © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: cerebellum, dentate nucleus, motor control, primates, 3D surface models.

It is currently popular to divide the primate and hominid dentate into an evolutionary older dorsal half and a newer ventral half (Leiner et al., 1993; Dum et al., 2002). A number of recent fMRI studies use this demarcation in their studies to define regions of interest and then relate the activity in these regions to various network patterns via functional connectivity studies (Habas et al., 2009; Granziera et al., 2009). The division of the dentate is thought to reflect the emergence of a cerebellofrontal projection and the enhancement of specifically human cognitive functions mediated by the prefrontal cortex such as language. The proposed ventral–dorsal division of the dentate is not new. Dow (1942) based a division into dorsal and ventral parts on older morphological, embryological (Weidenreich, 1899; Brun, 1918), myelinogenetic (van Valkenburg, 1912) and iron-staining studies (Gans, 1924). The morphological differentiation was based on the thicker (macrogyric) folds in the ventral part with smaller neurons (Gans, 1924) and thinner (microgyric) folds in the dorsal part of the nucleus (summarized by Dow, 1942). In a more recent study (Matano, 2001), the border between a dorsal and ventral part was placed simply at the midpoint of the dorso–ventral length. Using this criterion, it was found that the size of the ventral half increases in the ascending series of species from apes to humans.

EXPERIMENTAL PROCEDURES

Four human cerebella were obtained from the Witelson Normal Brain Collection (Witelson and McCulloch, 1991). All had been stored in 10% formalin. The cerebella were dissected away from the brainstem and cut into two halves along the midsagittal plane. They were then cryoprotected in 15% and then 30% sucrose in 10% formalin, embedded in an albumin–gelatin matrix and stored in 30% sucrose/10% formalin until sectioning. Serial sections in the parasagittal plane were collected and stored at 4 °C in 5% formalin. Sections every 400 μm apart were mounted on gelled glass slides, and stained for Nissl substance with Cresyl Violet. Slides were scanned at 1200 dpi on a Hewlett–Packard 3500c scanner and grayscale images were saved. The cerebellum of a Macaca *mulatta* (obtained from the Max Planck Institute for biological Cybernetics; the animal had been perfused with 4% paraformaldehyde and the brain cryoprotected in 30% sucrose in paraformaldehyde) was sectioned serially in the coronal plane at 60 μm. Sections were stained with Cresyl Violet. To make the 3D models, sections were aligned with the software Amira (Amira 4.1.1, Mercury Computer Systems, Chelmsford, USA). The overlying cerebellar cortex was used for alignment. We also used 3D reconstructions of the cerebellar cortex (granular layer) to align the section stack and the dentate model to the cardinal planes. In the case of the macaque the atlas of Snider and Lee (1961) was used for assistance. The contours of the dentate were traced and 3D surface models were also produced with Amira. To obtain the thickness of such a complex folded structure we applied the following technique. Two surfaces were created. The first surface enveloped the outer dentate contour and the second the inner (hillar) contour. To calculate the thickness we then obtained for every point along the inner surface mesh the distance to the nearest point on the outer surface mesh. The distribution of distances was then normalized to the maximal count (see Fig. 2).

RESULTS AND DISCUSSION

We wished to validate the proposed division of the human dentate into structurally unique dorsal and ventral parts.

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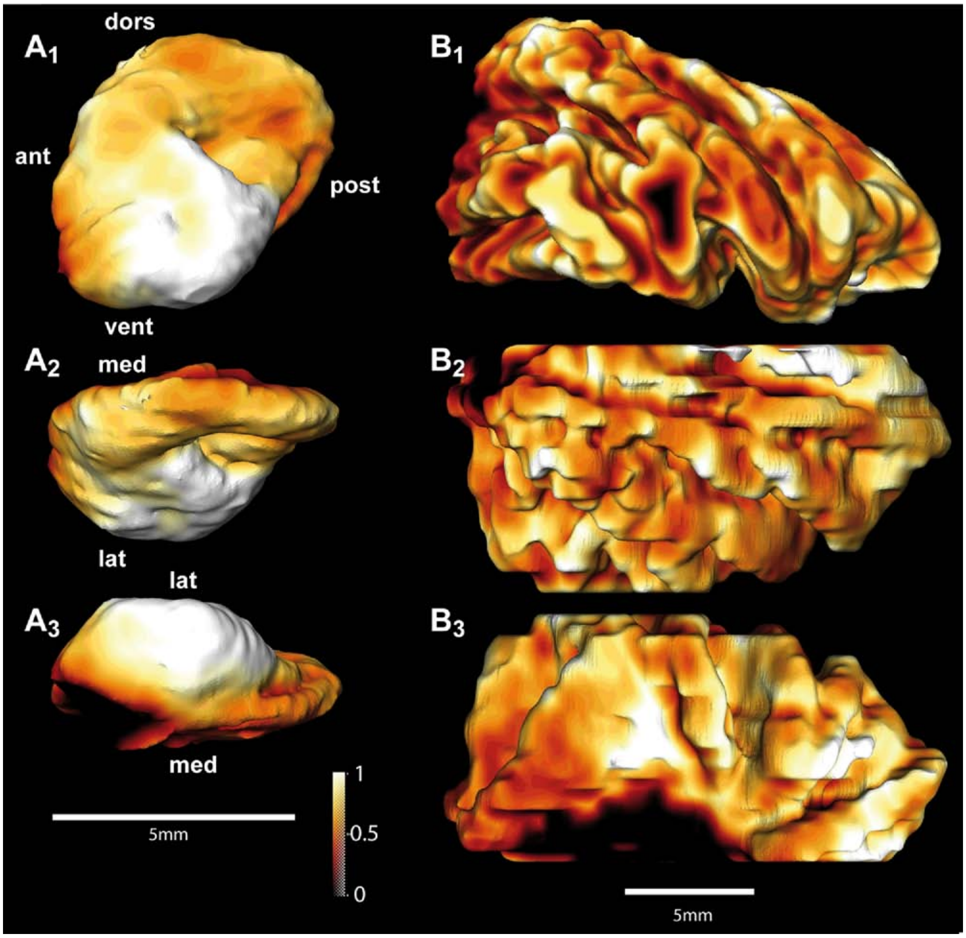

Fig. 1. Surface reconstructions of the lateral nucleus of the macaque (A_{1-3}) and of the human (the dentate, B_{1-3}). Overlaid on the surfaces is the thickness of the lamina at the respective site color coded with white depicting thicker regions (see color bar). Clearly a thicker macrogyric part can be discerned in the ventrolateral region of the macaque. This is not the case in the human dentate. The volumes obtained for the macaque dentate was 29 mm^3 and for the human 358 mm^3, the surfaces were 99 and 1219 mm^2, respectively. (A_1, B_1) lateral view; (A_2, B_2) dorsal view; (A_3, B_3) ventral view. Scale bars: 5 mm.

We therefore quantified the dentate lamina thickness as this is the most salient distinguishing morphological parameter used so far (Voogd et al., 1990). We built a detailed three dimensional model of the human dentate from serial Nissl-stained sections (Fig. 1B_{1-3}), and compared this to a model of the lateral nucleus (the equivalent of the dentate in monkeys) of the rhesus monkey (Fig. 1A, B). In the macaque, the model shows a thicker (macrogyric) part located in the ventro–lateral and posterior region of the lateral nucleus (Fig. 1A_{1-3}), as expected. This is much less evident for the human dentate. There is a thicker region on the ventral surface (Fig. 1B_3) of the human dentate, but this is more limited in size than expected, and more heterogeneous (showing regions of variable thickness) compared to the macaque. A plot of the thicknesses of the dentate confirms this observation (Fig. 2A). For the human, the peak thickness is shifted to 0.55 mm compared to the peak for the monkey of 0.7 mm (Fig. 2A). More importantly, laminar thicknesses larger than 0.8 mm corresponding to the monkey's ventral region, are absent in the human dentate.

The human 3D dentate model reveals an additional feature. As one follows the folds on a curved trajectory from medial to lateral they appear to get broader (Figs. 1B and 3C). This can also be noted in the wax-model of the dentate of Ariëns Kappers (1921) and in the model by Voogd et al. (1990). However, this is not due to the emergence of folds with thicker laminae (see Fig. 2B) but instead to the emergence of secondary folding that make the primary folds seem broader.

The main result of this study is that the major morphological feature accompanying the increased size and different shape of the human dentate is an increase in surface area of the dentate as a whole, and not a selective increase in size of a ventral subdivision. There is also a much more complex folding pattern and a thinning of laminae in human compared to macaque. This conclusion is in agreement with previous suggestions that the development and increase of surfaces in brains is an indicator of an increase in the computational capacity (Sultan, 2002; Glickstein et al., in press). A division of the lateral nucleus into dorsal and ventral regions with different lamellar thick-

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