Evidence for a Motor Somatotopy in the Cerebellar Dentate Nucleus—an fMRI Study in Humans

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Abstract: Previous anatomical studies in monkeys have shown that forelimb motor representation is located caudal to hindlimb representation within the dorso-rostral dentate nucleus. Here we investigate human dentate nucleus motor somatotopy by means of ultra-highfield (7 T) functional magnetic brain imaging (fMRI). Twenty five young healthy males participated in the study. Simple finger and foot movement tasks were performed to identify dentate nucleus motor areas. Recently developed normalization procedures for group analyses were used for the cerebellar cortex and the cerebellar dentate nucleus. Cortical activations were in good accordance with the known somatotopy of the human cerebellar cortex. Dentate nucleus activations following motor tasks were found in particular in the ipsilateral dorso-rostral nucleus. Activations were also present in other parts of the nucleus including the contralateral side, and there was some overlap between the body part representations. Within the ipsilateral dorso-rostral dentate, finger activations were located caudally compared to foot movement-related activations in fMRI group analysis. Likewise, the centre of gravity (COG) for the finger activation was more caudal than the COG of the foot activation across participants. A multivariate analysis of variance (MANOVA) on the *x*, *y*, and *z* coordinates of the COG indicated that this difference was significant ($P = 0.043$). These results indicate that in humans, the lower and upper limbs are arranged rostro-caudally in the dorsal aspect of the dentate nucleus, which is consistent with studies in non-human primates. *Hum Brain Mapp* 33:2741–2749, 2012. © 2011 Wiley Periodicals, Inc.

Key words: highfield; cerebellum; homunculus; movement; anatomy

Contract grant sponsor: German Research Foundation; Contract grant number: DFG Ti239/9-1; Contract grant sponsor: Marie Curie Initial Training Network “Cerebellar-Cortical Control: Cells, Circuits, Computation and Clinic”; Contract grant sponsor: IFORES grant of the University of Duisburg-Essen, Medical Faculty.

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Received for publication 7 January 2011; Revised 2 May 2011; Accepted 9 June 2011

DOI: 10.1002/hbm.21400

Published online 21 September 2011 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

While the somatotopy within the human cerebellar cortex, comprising at least two homunculi located in the anterior and posterior cerebellum, is well established [Grodd et al., 2001; Rijntjes et al., 1999], somatotopy within the human deep cerebellar nuclei is yet elusive. Animal studies in monkeys report a somatotopic organization of motor representations within the dentate and interposed (that is globose and emboliform in humans) nuclei. Although results differ to a certain extent depending on monkey species and applied methods, two features have been repeatedly reported: (1) the representation of the lower limb (hindlimb) is found more rostrally compared to the upper limb (forelimb) [Allen et al., 1978; Asanuma et al., 1983; Dum and Strick, 2003; Hoover and Strick, 1999; Lu et al., 2007; Rispal-Adel et al., 1982; Stanton, 1980; Thach et al., 1993; van Kan et al., 1993; Wiesendanger and Wiesendanger, 1985]; and (2) overlap of different body part representations can be found [Allen et al., 1978; Evrard and Craig, 2008; Lu et al., 2007; Rispal-Adel et al., 1982; van Kan et al., 1993; Wiesendanger and Wiesendanger, 1985]. Reports on the exact location of motor representation in the dentate nucleus, however, are mixed. Previous studies have reported that dentate projections to M1 (fore- and hindlimb representation) originate mainly from the dorso-rostral nucleus [Dum and Strick, 2003; Hoover and Strick, 1999; Lu et al., 2007], while others have suggested a more broadly distributed motor domain based on efferent connections to the thalamus [Evrard and Craig, 2008]. Likewise, Allen et al. [1978] found motor representation primarily located at the ventral pole of the dentate nucleus, and others reported that motor representation covers the entire nucleus [Asanuma et al., 1983; Thach et al., 1993]. Note that nomenclature differs between authors, e.g., the rostral-caudal axis [Dum and Strick, 2003; Hoover and Strick, 1999; Lu et al., 2007; Stanton, 1980] corresponds to the anterior-posterior axis [Allen et al., 1978; Asanuma et al., 1983; Thach et al., 1993; van Kan et al., 1993].

We asked the question whether or not a motor somatotopy can be found in the human dentate nucleus. Therefore, we applied ultra-highfield (7 T) fMRI in combination with a recently published improved normalization procedure for the dentate nucleus [Diedrichsen et al., 2011]. We hypothesize that there is a rostro-caudally arranged somatotopy within the more dorsal and rostral dentate nucleus.

METHODS

A total of 25 healthy male participants (mean age of 28.3 ± 6.4 years) were included. All participants were right-handed as assessed by the Edinburgh handedness scale [Oldfield, 1971]. Two participants were excluded because of movement artifacts (head translation >2 mm). Data of 23 participants (mean age 28.1 ± 6.3 years) were included in group statistical analysis. A whole-body 7 T MR scanner

(Magnetom 7 T, Siemens Healthcare, Erlangen, Germany) was used to acquire blood oxygenation level dependent (BOLD) contrast-weighted EPIs for functional scans. All fMRI images were acquired with an eight-channel transmit/receive head coil (Rapid Biomedical, Rimpar, Germany). Each EPI session consisted of 135 mosaic scans (mosaic scanning refers to a data format to store 3D images in a 2D grid or mosaic DICOM image file) with 45 slices, matrix 128×128 , TR = 3,000 ms, TE = 22 ms, FOV = 256 mm, GRAPPA R = 2, TA 6:54 min, flip angle between 49° and 78° (the excitation pulse angle α was chosen as close to the Ernst angle as permitted by the SAR monitor depending on subject weight and transmitter adjustment), bandwidth 1,562 Hz/pixel, sinusoidal readout gradient, slice thickness 1.9 mm, and voxel size = $2.0 \times 2.0 \times 1.9$ mm³ with 10% distance factor due to ascending mode. Distance factor refers to spacing between slices. This is necessary to avoid noise in adjoining slices because of cross excitation effects. Because of magnetization relaxation effects, the first five volumes in each session were discarded from further analysis. Scans covered the entire cerebellum. Commonly, fMRI studies use an anterior-to-posterior phase-encoding direction with axial slice orientation. In comparison to the homogeneous cerebrum, this direction cuts through many sharp tissue boundaries (i.e., air-bone) for inferior planes. Because of the stronger Nyquist ghosts in the phase-encoding direction at 7 T, artifacts in the cerebellum are common. To avoid these, the EPI images were acquired in coronal orientation with the phase-encoding direction feet $\gg$ head. No correction was performed for physiological noise (respiration, vessel pulsation).

In addition, a three-dimensional (3D) transverse volume of the entire brain was acquired using a T1-weighted magnetization prepared rapid acquisition gradient echo sequence (MPRAGE; 176 sagittal slices, TR = 3,500 ms, TE = 3.71 ms, TI = 1,100 ms, bandwidth 200 Hz/pixel, FOV = 256×176 mm², GRAPPA R = 2, TA 6:30 min, flip angle 8° , slice thickness 1 mm, and voxel size = $1 \times 1 \times 1$ mm³).

Experimental Conditions

A block design was used with seven 30-s rest and six 30-s active blocks (total of 135 scans). The participants had to perform simple finger and foot movement motor tasks on the right side. Each task was performed in a separate fMRI run. Prior to imaging, participants were briefly trained outside the scanner on how to perform each of the two tasks. In addition, a 30-s training block was done in the scanner before commencement of each of the six fMRI runs. The sequence of the tasks was randomized between participants.

For finger movement participants conducted a tapping task with their right index finger while their hand rested on their right thigh. Participants were asked to repeatedly move the index finger two times to the right side (using the maximum lateral movement range of their index finger

Figure 1.

Cerebellar cortical activations following finger (red) and foot (blue) movement performed with the right side plotted on the SUIT template in coronal slices [Diedrichsen, 2006], thresholded at $P < 0.005$ FDR corrected (threshold t value = 3.8, peak t value = 10). Lower row shows overlap between both conditions

(threshold t value = 3.8, peak t value = 3.8). Color code denotes t values. White numbers indicate y -coordinates. Latin numbers indicate cerebellar lobules. Right side of the image is right side of the brain. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

without wrist movement) and one time to the left side. Results for the finger tapping task have been published previously [Küper et al., 2011]. However, image processing and statistical analysis were different in the previous study and were chosen to compare 7 T fMRI to 1.5 T fMRI data. For foot movement participants had to move their right foot two times to the right side and one time to the left side using the ankle joint's maximum movement range. Participants were asked to perform the movements quickly; however, participants were allowed to perform the movements at their own pace.

Tasks and rest conditions were performed with the eyes open. An active block was started by visual presentation of the word "finger" or "foot," respectively, in the centre of the participants' visual field. During rest, a fixation cross was visually presented at the same location. Eye movements were not recorded. Visual stimuli were generated by a PC system running E-PRIME software (<http://www.pstnet.com/eprime.cfm>) and presented via a projector onto a screen. Visual images were viewed from a mirror mounted on the eight-channel head coil.

Image Analysis

The functional imaging data were analyzed using statistical parametric mapping (SPM5, Wellcome Department of

Cognitive Neurology, London, UK) implemented in Matlab (Matlab 7, The MathWorks, Natick, MA). First, EPI images were realigned to correct for head motion, resulting in creation of a mean EPI image. This image was then co-registered to the anatomical T1 image of the individual participant. The automatic co-registration was refined manually to ensure the fit of the cerebellar structures. For the statistical 1st level analyses, a general linear model [Friston et al., 1995] was then applied to the realigned, but otherwise unsmoothed, EPI images. The time series of each voxel was fitted with a corresponding task regressor that modeled a boxcar convolved with a canonical hemodynamic response function. A temporal highpass filter (cut-off 128 s) was used to correct for the low frequency drifts in the data, and serial autocorrelations were taken into account by means of an AR(1) correction. For each of the experimental tasks and control conditions, a significant change of the BOLD effect compared to the rest condition was tested by specifying the appropriate contrast.

Cerebellar Cortex

For the normalization of the cerebellar cortical data, the T1-weighted images were deformed to fit the spatially unbiased atlas template (SUIT) of the human cerebellum [Diedrichsen, 2006]. This non-linear deformation was then

Figure 2.

Significant dentate nucleus activation following motor tasks plotted on probabilistic dentate nucleus template [Diedrichsen et al., 2011], shown in axial slices (white numbers indicate z-coordinate). Finger movement related activation (left column) and foot related activation (middle column) are shown in red-yellow. Color code denotes t values (threshold 3.79, peak 5). Overlay of both movement tasks (finger = red, foot = blue) is shown in the right column. For the right column, threshold and peak t value are both 3.79 for better delineation between tasks. Ipsi = ipsilateral side (right), Contra = contralateral side (left); r = rostral, c = caudal. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

applied to each contrast image from the individual participants. The normalized images were then smoothed with a Gaussian kernel of 4-mm full width at half maximum (FWHM). Group analysis was performed at a significance level of $P < 0.005$ ($t(23) = 3.8$), false discovery rate (FDR) corrected for multiple comparisons. For visualization, t -maps from group analyses (Fig. 1) were plotted on a spatially unbiased cerebellar template [Diedrichsen, 2006].

Dentate Nucleus

The dentate nuclei were identified as hypointensities on the mean image and marked as the region of interest

(ROI) using MRICRON software (www.sph.sc.edu/comd/rorden/mricron/). For normalization, a modified version of the SUI method was used. This normalization algorithm tries to deform the T1 image so that it fits to the SUI template, while optimizing the overlap between the ROI and a dentate template that was developed by our group as an average of 23 healthy control subjects participating in another study [Diedrichsen et al., 2011]. This method ensures improved overlap between the nuclei of individual participants compared to standard SPM normalization, while preserving a good normalization of other structures. To avoid activation surrounding the dentate nucleus being smoothed into the ROI, the functional images were masked with the dentate ROI before normalization. The normalized functional data from the dentate nuclei were resampled at $1 \times 1 \times 1 \text{ mm}^3$ resolution and then smoothed with a 4-mm kernel FWHM. To improve the signal-to-noise ratio, smoothing was performed with a slightly larger kernel than recently recommended [2–3 mm kernel FWHM in Diedrichsen et al., 2011]. Physiological movements were not controlled for and likely increased noise.

Group analysis was performed at an uncorrected (unc.) threshold of $P = 0.0005$ ($t(23) = 3.79$), and a correction for multiple tests was achieved by adjusting the critical cluster size for this threshold. Because the search region was very small and the data only modestly smoothed, random field theory [Worsley et al., 1996] would not give a valid critical cluster size. A bootstrap analysis was therefore employed to determine the significance level for multiple tests [Hayasaka and Nichols, 2003]. Sets of 23 random samples were drawn (with replacement) from all contrast images, and each multiplied independently with 1 or -1 to randomize the sign. For each of these fake data sets, a t -map was calculated and the maximum t -value and cluster size were determined at the uncorrected threshold ($t(23) = 3.79$, $P = 0.0005$), searching both in the left and right dentate. Repeating this process 10,000 times, the threshold values were determined that would only occur in 5% of the random data sets. The corrected minimal cluster size was 4.2 mm^3 .

For visualization, t -maps from group analyses were plotted on a probabilistic dentate nucleus template (Fig. 2; [Diedrichsen et al., 2011]) and on a 3D surface reconstruction of the same probabilistic dentate nucleus template (Fig. 3) created with CARET software (<http://brainvis.wustl.edu/wiki/index.php/Caret>About>).

To test the somatotopic gradient statistically, one cannot simply rely on the location of the maxima in the group map. Rather, a measure of the location of the finger and foot activation in each participant is needed. Because the location of the maximum in each participant is inherently a very unstable measure, the centre of gravity (COG) of activation within the motor-related regions of the dentate nucleus was determined. To delineate this region, an ROI based on the averaged contrast for foot and hand movements (compared to rest) was defined and the largest cluster at a threshold of $t(23) = 3.79$ (0.0005 unc.) was found.

Figure 3.

Dentate nucleus motor activation plotted on 3D surface reconstruction. Color code denotes *t* values. Ipsi = ipsilateral side (right), Contra = contralateral side (left). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

An analysis using the OR combination of these two statistical maps at $t(23) > 4.5$ led to comparable results.

For each participant, each voxel in this region was then assigned to the hand or the foot region, depending on the condition for which it showed the higher activation. To reflect the size of the activation difference, a softmax (rather than a max) function was used. The softmax operator calculates the probability that the voxel belongs to the hand region ($P(\text{hand})$) based on the activation for the hand and foot (act_hand and act_foot):

$$P(\text{hand}) = \exp(\text{act_hand}) / [\exp(\text{act_hand}) + \exp(\text{act_foot})]$$

Similarly, the probability of each voxel within the motor-related region to be part of the foot region was defined as $P(\text{foot}) = 1 - P(\text{hand})$. In this way, if a voxel was equally activated for both hand and foot movements, $P(\text{hand}) = P(\text{foot}) = 0.5$. Voxels that were slightly more activated for the hand than for the foot would be assigned $P(\text{hand}) > P(\text{foot})$, and only voxels that were clearly more activated for the hand condition would get values close to $P(\text{hand}) = 1$ and $P(\text{foot}) = 0$.

The *x*-coordinate of the centre of gravity (COG) of the hand was then calculated as the average coordinate of the selected voxels, weighted by their probability:

$$\text{COG}_{\text{hand}}(x) = \sum_i p_i(\text{hand}) x_i / \sum_i p_i(\text{hand}).$$

The same was done for the *y*- and *z*-coordinates, and for the foot region. The 23 individual COGs were then con-

trasted using a one-factorial multivariate analysis of variance (MANOVA) for repeated measures.

RESULTS

Cerebellar Cortical Activation

Cerebellar cortical activation (Fig. 1, Table I) was detected bilaterally, though clearly accentuated on the ipsilateral side, in the known motor representation within the anterior (Lobules IV, V, VI) and posterior (Lobule VII, VIII, IX) cerebellum [Grodd et al., 2001; Rijntjes et al., 1999; Stoodley and Schmahmann, 2009].

Within the anterior cerebellum, foot movement related activation involved more rostral (anterior) parts (especially Lobule IV) compared to finger movement related activation (especially Lobule V). Additional activation was present in Lobule VI with some extension into Crus I for both motor tasks.

In the posterior cerebellum, highest activations for both tasks were found in Lobule VIIIa. Although largely focused on Lobules VIIIa and VIIIb, there was also activation present in Lobule VIIb for both tasks and additionally Lobule IX for foot movement.

Overlap between finger and foot related activation was observed within the ipsilateral anterior and posterior cerebellar cortex and especially within the contralateral anterior cerebellum, whereas no overlap was found in the contralateral posterior cerebellum.

TABLE I. Local activation maxima within the cerebellar cortex ($P < 0.005$ FDR corrected)

Task	x,y,z	Location	Cluster size (mm ³)	t -value
Finger movement	23, -51, -18	ipsi: <u>IV</u> , <u>V</u> , VI, CrI, white matter	25,354	11.88
		contra: <u>IV</u> , V, VI, CrI		
	26, -56, -50	ipsi: VIIb, <u>VIIIa</u> , VIIIb	4,012	7.65
	-9, -56, -29	contra: white matter	15	4.58
	-33, -56, -48	contra: VIIb	22	4.19
	-9, -47, -28	contra: white matter	12	4.18
Foot movement	-25, -64, -54	contra: VIIIa	8	3.99
	14, -38, -21	ipsi: <u>IV</u> , V, VI, CrI, VIIb, VIIIa, VIIIb, white matter	28,331	15.00
	-36, -62, -27	contra: <u>VI</u> , CrI	4,399	7.53
	-22, -40, -53	contra: VIIIb	213	5.27
	-15, -51, -36	contra: white matter	121	4.93
	-8, -56, -55	contra: IX	16	4.91
	-26, -33, -22	contra: <u>IV</u> , <u>V</u>	506	4.84
	-37, -42, -33	contra: VI	154	4.77
	-34, -53, -53	contra: <u>VIIIa</u> , VIIb	118	4.71
	-1, -56, -32	contra: IX, ipsi: IX	100	4.64
	5, -65, -43	ipsi: VIIIb	72	4.58
	-17, -70, -53	contra: VIIIa	9	4.24
	24, -68, -55	ipsi: VIIIa	11	4.24
	-10, -53, -28	contra: white matter	16	4.2
	14, -59, -46	ipsi: VIIIb	31	4.17
	-30, -61, -55	contra: VIIIa	14	4.01

Ipsi = ipsilateral (right), contra = contralateral (left).

Peak location is underlined when several lobules are involved.

Dentate Nucleus Activation

Motor representation

Motor related activation was detected bilaterally in the dentate nucleus, at an uncorrected threshold of $t(23) = 3.79$, $P < 0.0005$ (Figs. 2 and 3, Table II). Most significant activations (highest t values) were found ipsilaterally within the more dorsal and rostral nucleus for both movement conditions. When averaging both motor contrasts one suprathreshold cluster was observed, which was located within the ipsilateral more dorsal and rostral nucleus, suggesting that this area serves motor function.

Movement related activation, however, was not restricted to the dorso-rostral dentate but extended continuously into neighboring ventral parts at the rostral pole. In addition, one separate ipsilateral cluster was present for

both motor conditions involving ventral and caudal parts of the dentate. While the additional cluster was small for finger movement, it exhibited substantial size following foot movement. There was also a smaller contralateral caudal cluster detected for foot movement.

Contralateral activation was less significant with regard to t values but had considerable cluster size, in particular following foot movement. Within the dorsal dentate, contralateral activation was almost symmetrical with respect to ipsilateral activation.

Somatotopy

In the ipsilateral dentate nucleus, the peak activations for finger movement were located 6 mm more caudally (posterior) compared to foot movement (Figs. 2 and 3,

TABLE II. Local maxima of dentate nucleus activation

Task	Side	x,y,z	Cluster size	t -value
Finger movement	ipsilateral (right)	12, -56, -28	243 mm ³	5.44
	ipsilateral (right)	14, -63, -40	36 mm ³	4.18
	contralateral (left)	-12, -55, -29	27 mm ³	4.37
Foot movement	ipsilateral (right)	11, -50, -30	106 mm ³	5.34
	ipsilateral (right)	7, -61, -33	113 mm ³	5.28
	contralateral (left)	-17, -52, -38	150 mm ³	4.59
	contralateral (left)	-10, -58, -34	37 mm ³	4.18

Table II). The peak for the finger was at $y = -56$ and for the foot at $y = -50$. Thus, the group maps suggested a somatotopic representation in the dorso-rostral dentate nucleus motor area.

To test this observation statistically, a ROI of the dentate motor region was defined by averaging the contrast foot minus rest and finger minus rest. This map was thresholded at $t(23) = 3.79$ (0.0005 unc.), which revealed one suprathreshold ipsilateral cluster located in the dorso-rostral dentate comprising 135 mm³. This cluster was subsequently chosen as the ROI. Within this region the COG was then calculated for hand and foot activations for each subject (see Methods).

Across participants, the COG for the foot activation was more medial and rostral (anterior) than the COG of the hand activation. A MANOVA on the x , y , and z coordinates of the COG indicated that this difference was significant with a Wilks' lambda $\Lambda(1,22,3) = 0.67$, $P = 0.043$. Thus, our results confirm that the area of most movement-related activation in the dentate nucleus is located dorso-rostrally and has a somatotopic gradient between hand and foot movement.

DISCUSSION

The main findings of this study are: (1) motor activation in the human dentate nucleus takes place primarily in the dorso-rostral part ipsilaterally to the movement, but also involves other parts of the nucleus, (2) within the dorso-rostral dentate, foot motor representation is located more rostrally than finger motor representation, and (3) motor related activation can also be found contralaterally to movement. These results are in good accordance with findings of studies conducted in monkeys [Dum and Strick, 2003; Hoover and Strick, 1999; Lu et al., 2007; Rispal-Padel et al., 1982; Soteropoulos and Baker, 2008; van Kan et al., 1993].

Cerebellar Cortical Activation

Cerebellar cortical activation was found bilaterally in the two characteristic regions of body representation which have been described in previous human fMRI studies, one within the anterior cerebellum and one within the posterior cerebellar lobe [Grodde et al., 2001; Rijntjes et al., 1999; Stoodley et al., 2009]. Consistent with these previous fMRI studies, finger-related activation was found caudally (posteriorly) to activation following foot movement within the anterior cerebellum. A second body representation was found in Lobule VIII in the posterior lobe.

We also observed extension of activation of the anterior representation into Lobules VI and Crus I. Recently, activation of Lobule VI and Crus I was linked to increased complexity in motor tasks. Within these lobules, an additional somatotopic organization has been proposed with foot activation being located caudally (posteriorly) and laterally compared to finger activation [Schlerf et al., 2010].

Likewise, we observed foot activation extending to more lateral and caudal parts (Crus I), although finger and foot activations largely overlapped in this area.

Dentate Nucleus Activation

Location of motor representation and somatotopy

Motor activation was primarily found within the dorsal part of the ipsilateral dentate nucleus for both motor tasks. When averaging both motor contrasts, only one significant cluster remained. This cluster was located in the ipsilateral dorso-rostral dentate. This finding is in agreement with anatomical data obtained with retrograde axonal transport of neurotropic viruses injected in different body representations of M1 [Dum et al., 2003; Lu et al., 2007]. Dentate output to M1 for the upper and lower limb was found to originate from more dorsal and rostral parts while more ventral parts of the dentate projected to cerebral areas known to be concerned with cognitive functions, e.g., working memory or visuospatial abilities [Dum and Strick, 2003; Strick et al., 2009]. These dentate areas also show different antigenic properties [Pimenta et al., 2001]. Based on these findings, Strick et al. postulated that the dentate nucleus can be subdivided into a dorsal motor domain and a ventral non-motor domain. In a comparative study including humans and other non-human primates, selective enlargement of the ventral dentate portion during evolution was reported [Matano, 2001] and it was suggested that cognitive function would be mediated by the ventral half of the nucleus (but see also Sultan et al. [2010] for a different view).

Recent fMRI studies [Küper et al., 2011; Marvel and Desmond, 2010] have provided evidence that a similar compartmentalization may be present in the human dentate nucleus. In the current study, however, motor related activation was not restricted to the dorso-rostral dentate nucleus but also comprised caudal and ventral parts of the nucleus. Strict subdivision of the dentate nucleus into a pure motor and pure cognitive subdivision, however, may be an oversimplification. In motor tasks of increasing complexity, motor planning becomes more important and may involve parts of the cerebellar nuclei (and cortex) different to primary body representation. As stated above, Schlerf et al. [2010] reported a novel cerebellar cortical somatotopy located in Crus I, which was exclusively elicited following complex (but not simple) movement tasks. Efferent connections to M1 have been identified originating not only from the dorso-rostral but also from the ventro-caudal regions in animal studies, although in lesser quantity compared to the dorso-rostral dentate [Lu et al., 2007]. One may argue, however, that functions which are considered non-motor (attention, working memory) play an increasing role in complex motor tasks.

The present results appear to be at variance with earlier findings of our group [Dimitrova et al., 2006]. Using 1.5 T MRI, we found prominent ventral dentate nucleus activation but no dorsal activation in a finger tapping task. No

dentate activation was detectable following foot movement. Finger tapping peak maxima in that study were found in the cerebellar cortex and extended continuously into the cerebellar nuclei region [see Fig. 5 in Dimitrova et al., 2006]. However, normalization was performed using standard SPM methods, which suffer from poor overlap of the dentate nucleus of different participants in a group analysis. Furthermore, there is a substantial danger that reported activations of the dentate may have been due to activation from surrounding gray matter structures smoothed into the nucleus (Type II error), especially given that a smoothing kernel of 6 mm FWHM was used. In fact, a new analysis of these data applying the improved normalization protocol used in the current study did not lead to any statistically significant activation within the dentate nucleus [Küper et al., 2011].

Somatotopy

Monkey studies show consistently that the dentate nucleus forelimb motor representation is located caudally (posteriorly) from the hindlimb motor representation [Allen et al., 1978; Asanuma et al., 1983; Dum and Strick, 2003; Hoover and Strick et al., 1999; Lu et al., 2007; Rispa-Padel et al., 1982; Thach et al., 1993; van Kan et al., 1993]. Likewise, comparing finger and foot movement during fMRI, we found peak activation in group analysis more caudally for finger compared to foot movement on both sides. In the current human fMRI study, subsequent statistical analyses based on individual centres of gravity located in the ipsilateral dentate nucleus motor region confirmed a significant somatotopic gradient.

Group analysis of dentate nucleus activation, on the other hand, suggests considerable overlap between finger and foot movement related activation. This finding is in good accordance with anatomical monkey data showing overlapping representation of the forelimb and hindlimb [Allen et al., 1978; Evrard and Craig, 2008; Lu et al., 2007; Rispa-Padel et al., 1982; van Kan et al., 1993; Wiesendanger and Wiesendanger, 1985] and parallels overlap between limb motor representations found in the human cerebellar cortex in the present and previous fMRI studies [Rijntjes et al., 1999]. In a recent retrograde tracing study, Evrard and Craig [2008] reported that dentate neurons related to upper or lower limb motor function were inhomogeneously dispersed and formed dense clusters intermixed with scattered patches of sparse labelling overlapping with one another. Likewise, some dentate neurons were found to be responsive to both fore- and hindlimb movement [van Kan et al., 1993], and neuronal stimulation of a single dentate neuron can trigger movement of different body parts simultaneously [Rispa-Padel et al., 1982]. Furthermore, the sensory receptive fields of dentate nucleus neurons in rats were shown to be large, covering the ipsi- and contralateral face and forepaws [Rowland and Jaeger, 2005].

Based on fMRI studies, however, it is difficult to provide convincing proof of overlap. Overlapping activation may

simply be a consequence of the statistical analysis procedure. That is, motor representations could be completely separated within each participant, but variable in their location, so that in the group map this could generate an overlap. Image smoothing can further add to the creation of an artificial overlap. Further reasons for artificial overlap may arise from the spatial limitations of the physiological BOLD point spread function during fMRI acquisition [Polimeni et al., 2010]. Ultra-highfield fMRI, however, has been shown to have narrower BOLD spread compared to 1.5T or 3T fMRI [Shmuel et al., 2007], suggesting less associated artificial overlap.

Contralateral dentate nucleus activation

Both human functional imaging studies [Cui et al., 2000; Ellerman et al., 1994; Jäncke et al., 1999] and neurophysiological studies in monkeys [Greger et al., 2004; MacKay, 1988; Soteropoulos and Baker, 2008] support the view that unilateral movements can be influenced by the ipsilateral and contralateral cerebellum. An increasing number of behavioural studies have shown that movement impairment following unilateral cerebellar damage is not restricted to the ipsilesional side [Boyd and Winstein, 2004; Fisher et al., 2006; Immisch et al., 2003]. Interestingly, in a recent study conducted in macaque monkeys, cerebellar nuclei firing patterns were shown to be responsive to movement of the contralateral forelimb [Soteropoulos and Baker, 2008]. In addition, electrical stimulation of the cerebellar nuclei elicited bilateral muscle responses in that study. Hence, contralateral activation of the dentate nucleus (and the cerebellar cortex) may not be surprising. Activations of the contralateral dentate nucleus were most significant in the more dorsal and rostral nucleus, which is in good accordance with the prominent dorso-rostral activations of the ipsilateral dentate. Our results point to a cerebellar influence on contralateral movement.

CONCLUSIONS

Ultra highfield (7 T) fMRI revealed that the human cerebellar dentate nucleus shares features of somatotopic organization that were previously described in monkeys. Motor representation resides in particular within the ipsilateral dorso-rostral dentate nucleus with a rostro-caudal arrangement of foot and hand representations.

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