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CEREBELLAR OUTPUT CHANNELS

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The cerebellum has long been regarded as involved in the control of movement, in part through its connections with the cerebral cortex. These connections were thought to combine inputs from widespread regions of the cerebral cortex and "funnel" them into the motor system at the level of the primary motor cortex. Retrograde transneuronal transport of herpes simplex virus type 1 has recently been used to identify areas of the cerebral cortex that are "directly" influenced by the output of the cerebellum. Results suggest that cerebellar output projects via the thalamus to multiple cortical areas, including premotor and prefrontal cortex, as well as the primary motor cortex. In addition, the projections to different cortical areas appear to originate from distinct regions of the deep cerebellar nuclei. These observations have led to the proposal that cerebellar output is composed of a number of separate "output channels." Evidence from functional imaging studies in humans and single neuron recording studies in monkeys suggests that individual output channels are concerned with different aspects of motor or cognitive behavior.

I. Introduction

It is well established that inputs to the cerebellum arise from multiple areas of the cerebral cortex, including portions of the frontal, parietal,

and temporal lobes (e.g., Brodal, 1978; Vilensky and Van Hoesen, 1981; Leichnetz *et al.*, 1984; Glickstein *et al.*, 1985; Schmahmann and Pandya, 1991, 1993, 1995). However, the output of the cerebellum from the deep nuclei was thought to terminate in a single region of the ventrolateral thalamus (e.g., Kemp and Powell, 1971; Asanuma *et al.*, 1983). This thalamic region was believed to project exclusively upon a single cortical area, the primary motor cortex (M1). Thus, according to this view, the function of cerebellar loops with the cerebral cortex was to collect information from widespread areas of cerebral cortex and "funnel" this information into the motor system for use in initiating movement and defining movement parameters (e.g., Evarts and Thach, 1969; Kemp and Powell, 1971; Allen and Tsukahara, 1974; Brooks and Thach, 1981; Asanuma *et al.*, 1983; Ito, 1984).

A number of observations have led some investigators to challenge this point of view. For example, Leiner *et al.* (1987, 1989, 1991, 1993, and this volume) have suggested that cerebellar output is directed to prefrontal, as well as motor, areas of the cerebral cortex. They noted that, in humans and apes, the dentate nucleus of the cerebellum appears to have increased in size in parallel with the frontal lobe. They argued that this enlargement of the dentate has enabled it to expand its influence beyond the primary motor cortex. In support of their proposal, it is now apparent that cerebellar projections to the thalamus are not limited to a single region of the ventrolateral thalamus, but target other thalamic nuclei as well (e.g., Percheron, 1977; Stanton, 1980; Kalil, 1981; Yamamoto *et al.*, 1992). Some of these thalamic nuclei project to cortical areas other than the primary motor cortex (e.g., Kievit and Kuypers, 1977; Miyata and Sasaki, 1983; Schell and Strick, 1984; Wiesendanger and Wiesendanger, 1985a; Goldman-Rakic and Porrino, 1985; Matelli *et al.*, 1989; Schmahmann and Pandya, 1990; Barbas *et al.*, 1991; Yamamoto *et al.*, 1992; Rouiller, *et al.*, 1994; Lynch *et al.*, 1994; Middleton and Strick, 1994).

Clearly, one of the major unresolved issues of cerebro-cerebellar circuitry is defining the cortical areas that are the targets of cerebellar output. If the cerebellum is to influence cognition or perception, as well as motor control, it must do so through projections from the deep nuclei to thalamocortical circuits concerned with these aspects of behavior. Thus, it is not sufficient to show that the cerebellum receives input from diverse cortical areas. Others have argued that such input functions simply to guide movement (e.g., Evarts and Thach, 1969; Kemp and Powell, 1971; Allen and Tsukahara, 1974; Brooks and Thach, 1981; Asanuma *et al.*, 1983). Instead, the anatomical argument for a cerebellar influence on activities other than the control of movement parameters must be based on the demonstration that cerebellar output targets diverse areas of cerebral cortex such as premotor, prefrontal, and posterior parietal cortex (see also Sasaki *et al.*, 1976, 1979).

In the past, a number of technical limitations have made it difficult to define cerebello-thalamocortical circuits. For example, most studies which examined the pattern of cerebellar terminations in the thalamus did not determine the cortical targets of these thalamic nuclei (however, see Hendry, *et al.*, 1979; Yamamoto *et al.*, 1992; Rouiller *et al.*, 1994). In addition, the lack of standard criteria for defining thalamic borders and a confusing thalamic nomenclature have made comparison of the results from different studies difficult. Consequently, with few exceptions, it has not been possible to determine the full extent of the cortex "directly" influenced by cerebellar output.

We have developed a tracing technique, transneuronal transport of herpes simplex virus type 1 (HSV1), which overcomes many of these problems (see Zemanick *et al.*, 1991; Strick and Card, 1992). This chapter reviews the rationale for using HSV1 as a transneuronal tracer and then presents some recent findings on the organization of cerebellar projections to the frontal lobe. These results indicate that cerebellar output targets not only the primary motor cortex, but also several areas of premotor, oculomotor, and prefrontal cortex. In addition, the projections to these cortical areas appear to originate from distinct regions of the cerebellar nuclei. Thus, we propose that the output from the cerebellum, and specifically that from the dentate, contains multiple "output channels," each of which projects to a distinct cortical area (Strick *et al.*, 1993; Middleton and Strick, 1994, 1996). Section III presents some of our physiological observations that indicate individual output channels are concerned with different aspects of motor or cognitive behavior (Mushiake and Strick, 1993, 1995; Strick *et al.*, 1993; Kim *et al.*, 1994).

II. Anatomical Studies

Transneuronal transport of HSV1 provides a novel method for labeling a chain of synaptically linked neurons (for references and review see Zemanick *et al.*, 1991; Strick and Card, 1992). In fact, this technique is capable of identifying circuits at least three neurons in length (Hoover and Strick, 1993b). In our anatomical studies, we have employed two different strains of HSV1, the H129 and McIntrye-B strains. To test the transport characteristics of these strains, we made localized injections into the arm area of the primary motor cortex of cebus monkey (Figs. 1 and 2). We found that the

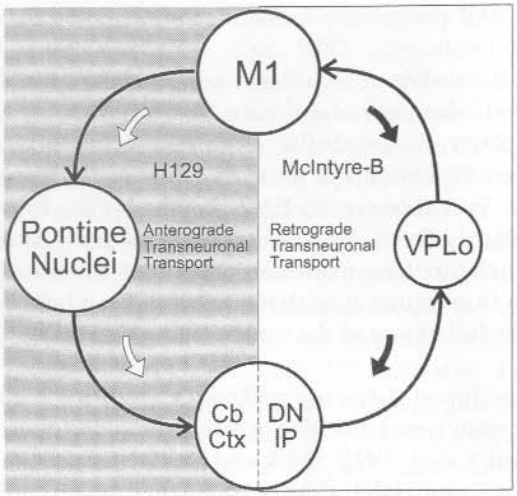

FIG. 1. Patterns of HSV1 transneuronal transport in cerebellar circuits. Different strains of HSV1 are transported transneuronally in different directions. The H129 strain is transported transneuronally in the anterograde direction. After injections of this strain into the primary motor cortex (M1), virus moves from the injection site to label second-order neurons in the pontine nuclei, and then third-order neurons in the cerebellar cortex (Cb Ctx) and the dentate (DN) and interpositus (IP) nuclei. In contrast, the McIntyre-B strain is transported transneuronally in the retrograde direction. After injections of the McIntyre-B strain into M1, virus moves from the injection site to label first-order neurons in the ventrolateral thalamus (VPLo), and then second-order neurons in DN and IP.

H129 and McIntyre-B strains are transported transneuronally in different directions (Zemanick *et al.*, 1991) (Fig. 1).

The H129 strain is transported transneuronally in the anterograde direction. Three days after injections of this virus into the arm area of M1, virus was transported from "first-order" neurons in the injection site to "second-order" neurons in regions of the pontine nuclei known to receive input from the arm area of M1 (Fig. 3A) (e.g., Brodal, 1978; Glickstein *et al.*, 1985). Five days after these injections, multiple patches of "third-order" neurons, labeled by anterograde transneuronal transport, were found in the cerebellar cortex. These patches were located in the granular layer and contained two types of labeled neurons: granule and Golgi cells (Fig. 3B). Both cell types are known to be contacted by mossy fiber afferents that project to the cerebellar cortex from the pontine nuclei (e.g., Allen and Tsukahara, 1974; Brooks and Thach, 1981; Ito, 1984). The majority of the labeled patches were located in vermal and hemispheric lobules V and VI, in and adjacent to the primary fissure (Figs. 3C and 4). Separate labeled patches were found posteriorly in the paramedian lobule (VIIIA) and laterally in lobule VIIB (Figs. 3C and 4).

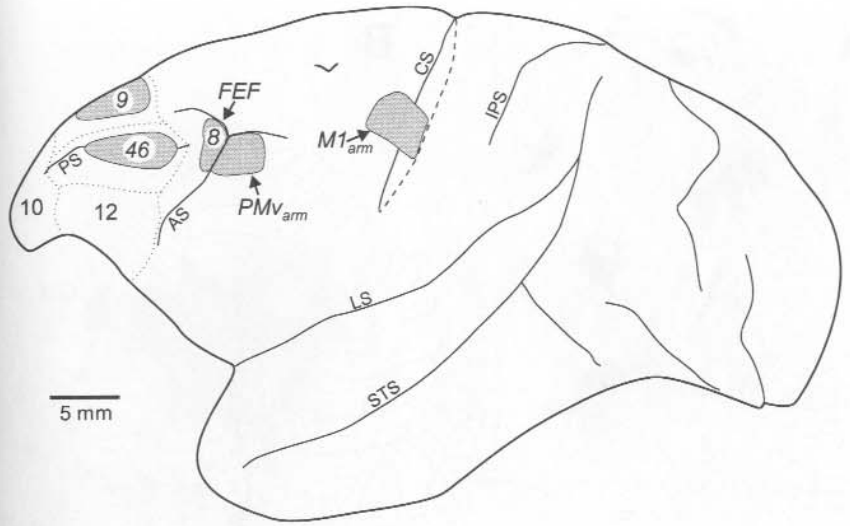

FIG. 2. Location of virus injection sites in the cerebral cortex. Lateral view of a cebus monkey brain. The shaded areas indicate the spread of HSV1 from injections into each cortical area. The numbers 8, 9, 10, 12, and 46 refer to cytoarchitectonic areas of the frontal lobe according to Walker (1940). The dotted lines define the borders between areas. AS, arcuate sulcus; CS, central sulcus; FEF, frontal eye field; IPS, intraparietal sulcus; LS, lateral sulcus; $M1_{arm}$, arm region of the primary motor cortex; PMv_{arm}, arm region of the ventral premotor area; PS, principal sulcus; STS, superior temporal sulcus.

Some labeled neurons were also found in portions of the dentate and interpositus nuclei. Evidence shows that the pontine nuclei project directly to the deep cerebellar nuclei in cats (Shinoda *et al.*, 1987); a similar pathway is thought to exist in primates. Thus, we found labeled neurons at third-order sites where one might expect to see them based on the results of prior studies using conventional tracing methods. In summary, the regions of cerebellar cortex and deep nuclei containing labeled neurons correlated well with the sites where evoked potentials have been recorded after stimulation of the arm area of the primary motor cortex (e.g., Sasaki *et al.*, 1977). These results suggest that it will be possible to define how many areas of the cerebral cortex map onto the cerebellar cortex and deep nuclei using the H129 strain as an anterograde transneuronal tracer.

In contrast to the H129 strain, the McIntyre-B strain of HSV1 is transported transneuronally in the retrograde direction (Zemanick *et al.*, 1991; Hoover and Strick, 1993a,b; Middleton and Strick, 1994) (Fig. 1). Three days after injections of this virus into the arm area of M1 (Fig. 2), many labeled neurons were found in subdivisions of the ventrolateral thalamus that are known to innervate M1 (Fig. 5A), such as the nucleus ventralis

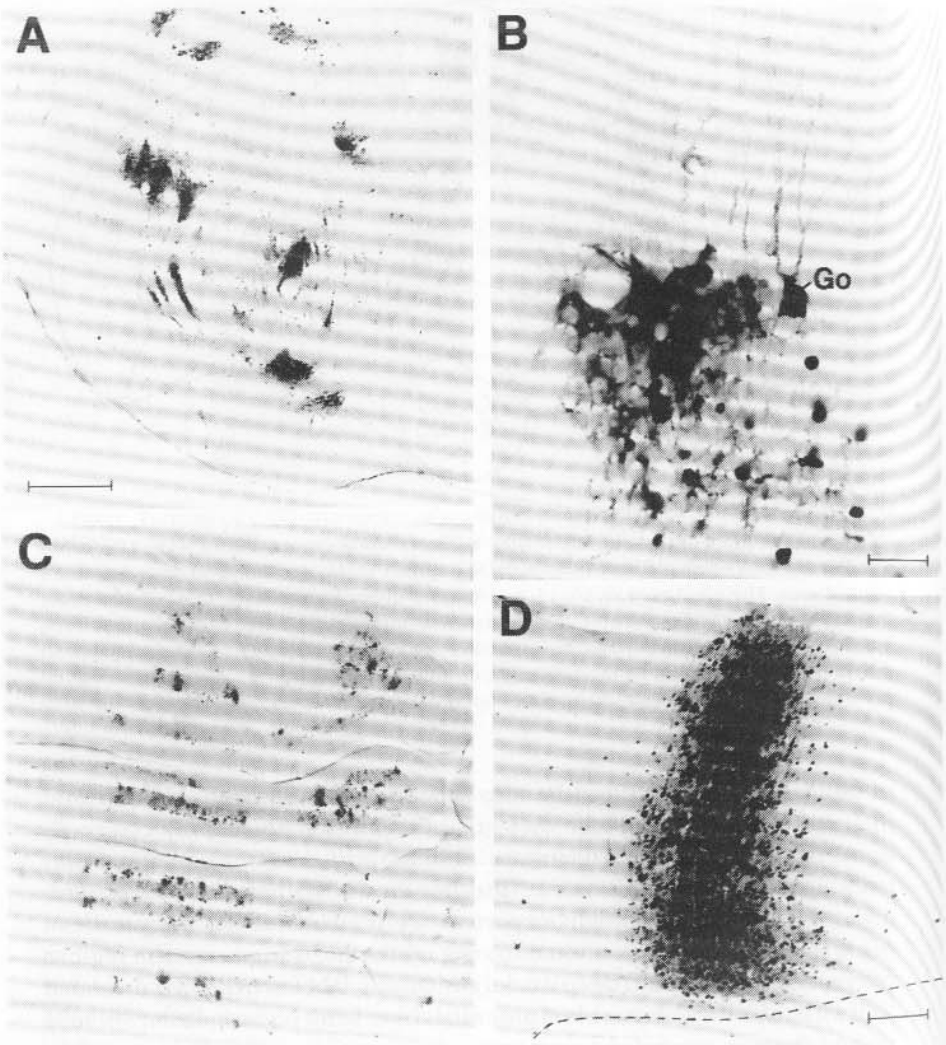

FIG. 3. Neurons labeled by anterograde transneuronal transport of HSV1 (H129) from M1. (**A**) Labeled neurons in the pontine nuclei (scale bar, 1 mm). (**B**) A patch of labeled granule cells and a Golgi cell (Go) in cerebellar cortex (scale bar, 30 μm). (**C**) Multiple patches of labeled neurons in the granular layer of cerebellar cortex (scale in A). (**D**) A "column" of labeled neurons in cerebral cortex buried within the dorsal bank of the cingulate sulcus. The dashed line indicates the border between white and gray matter (scale bar, 300 μm). (From Zemanick *et al.*, 1991.)

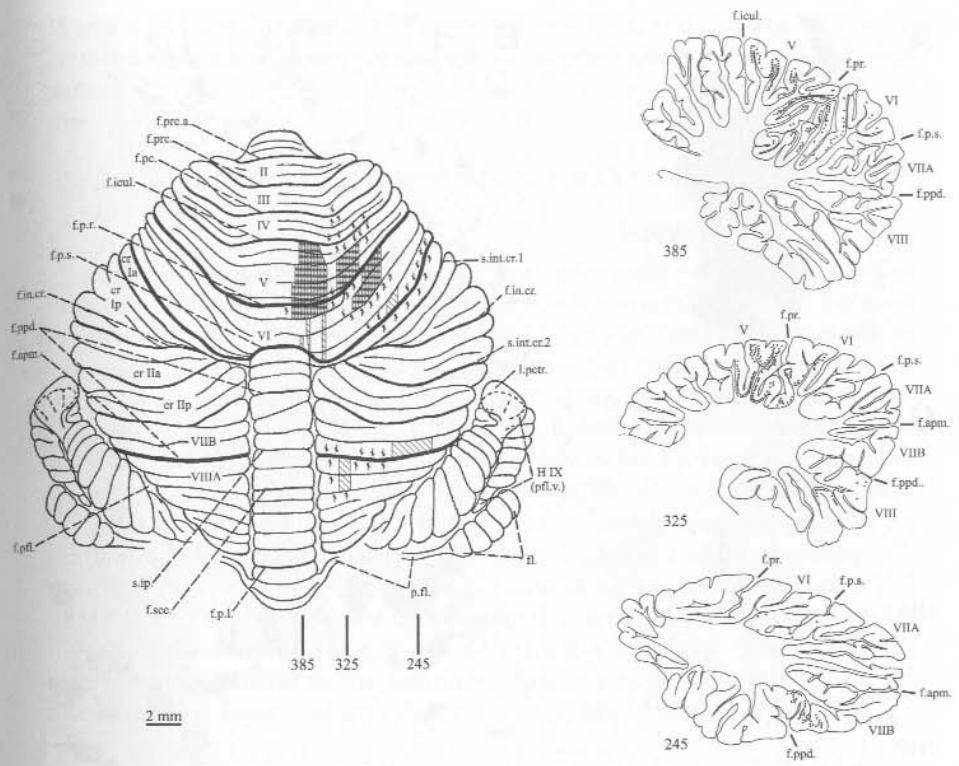

FIG. 4. Distribution of labeled neurons in cerebellar cortex after anterograde transneuronal transport of HSV-1 (H129) from the "arm area" of the primary motor cortex. (Left) Surface reconstruction of the distribution of labeled neurons found on the surface of the cerebellar cortex. The relative density and location of cells are indicated by the density and location of the cross-hatching. Small arrows indicate the location of labeled regions buried within fissures. The lines at the bottom of the figure indicate the location of the three sagittal sections shown on the right. The flattened view of cerebellar cortex and abbreviations used are adapted from Larsell (1970). (Right) Plots of labeled neurons in three sagittal sections taken from vermal (385), intermediate (325), and lateral (245) regions of cerebellar cortex. The small dots indicate the relative density and distribution of labeled neurons.

posterior lateralis pars oralis (VPLo) and nucleus ventralis lateralis pars oralis (VLo) of Olszewski (1952) (for references and review, see Holsapple *et al.*, 1991). Five days after these injections, virus was transported transneuronally in the retrograde direction from first-order neurons in the ventrolateral thalamus to second-order neurons in output nuclei of the cerebellum (i.e., the dentate and interpositus) and the basal ganglia (e.g., the internal segment of the globus pallidus) (Figs. 5B–5D).

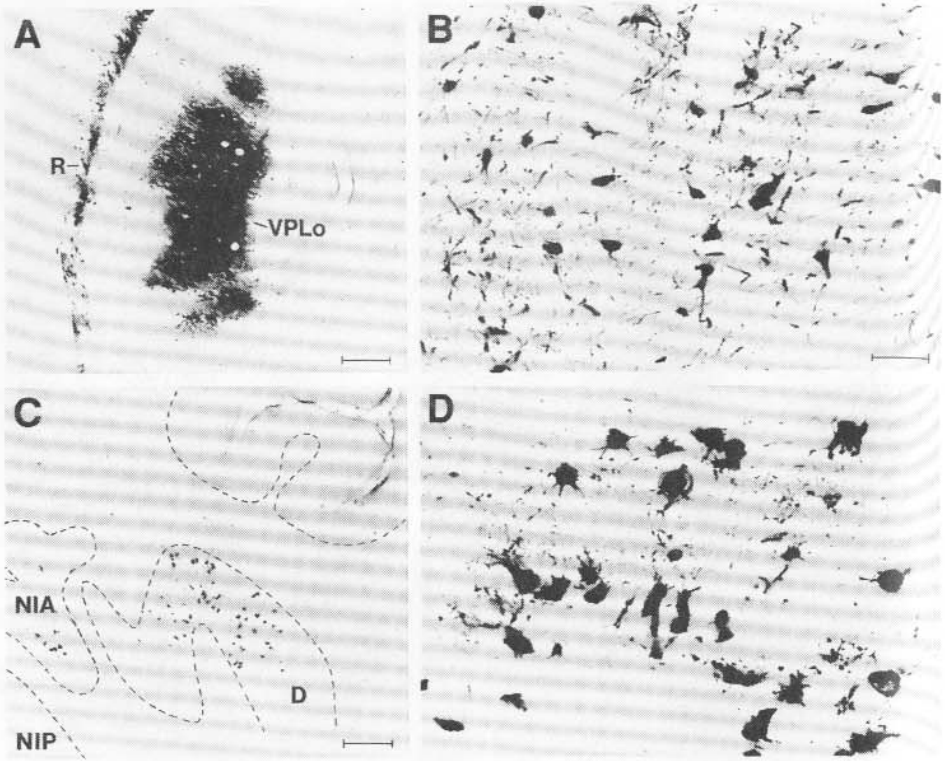

FIG. 5. Neurons labeled by retrograde transneuronal transport of HSV1 (McIntyre-B) from M1. (**A**) Ventrolateral thalamus (VPLo) and the reticular nucleus (R) (scale bar, 1 mm). (**B**) Internal segment of the globus pallidus (scale bar, 100 μm). (**C**) Deep cerebellar nuclei. Dashed lines outline the dentate (D), anterior interpositus (NIA), and posterior interpositus (NIP) nuclei (lower left) and a portion of cerebellar cortex (upper right) (scale bar, 500 μm). No labeled neurons were found in the posterior interpositus (NIP). (**D**) Dentate nucleus (scale in B). (From Zemanick *et al.*, 1991.)

Based on these results, we have used the labeling of second-order neurons by retrograde transneuronal transport of the McIntyre-B strain to map the origin of cerebellar (and basal ganglia) input to different cortical areas (Zemanick *et al.*, 1991; Hoover and Strick, 1993a; Strick *et al.*, 1993; Lynch *et al.*, 1994; Middleton and Strick, 1994). The following sections describe some of our observations on cerebellar projections to the arm representations of the primary motor cortex (area 4) and ventral premotor area (PMv) (area 6), the frontal eye field (FEF) (area 8), and two regions in the prefrontal cortex (areas 9 and 46) (Fig. 1) (Hoover and Strick, 1993a; Strick *et al.*, 1993; Lynch *et al.*, 1994; Middleton and Strick, 1994, 1996).

Virus injections into the arm areas of M1 and PMv, and into the FEF, were made after each area was physiologically mapped using intracortical stimulation.

A. Cerebellar Output to Skeletomotor and Oculomotor Areas of Cerebral Cortex

Specific portions of the dentate and interpositus contained labeled neurons following injections of McIntrye-B into the arm area of M1. Labeled neurons in the interpositus were located largely in caudal portions of the anterior division of this nucleus. Labeled neurons in the dentate were restricted to dorsal portions of the nucleus at mid rostrocaudal levels (Figs. 5C and 5D and Fig. 6, "$M1_{arm}$"). These regions of the dentate and interpositus are comparable to the sites where neuron activity related to arm movements has been recorded (e.g., Thach, 1978; Wetts *et al.*, 1985; van Kan *et al.*, 1993). Thus, the arm area of the primary motor cortex appears to be influenced by localized "arm areas" in the dentate and interpositus.

Injections of the McIntyre-B strain into the arm representation of the PMv (Fig. 2) labeled many neurons in the dentate, at mid rostrocaudal levels of the nucleus (Figs. 5 and 6) (Strick *et al.*, 1993). These neurons were located ventral to the region of the dentate that contained labeled neurons after injections into the arm area of M1 (compare Fig. 6, "$M1_{arm}$"

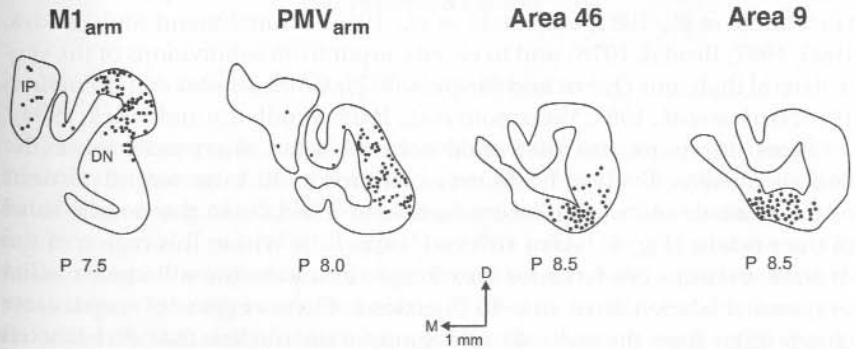

FIG. 6. Origin of cerebellar projections to M1, PMv, area 46, and area 9. Representative coronal sections through the dentate and/or interpositus nuclei of animals that received injections of the McIntyre-B strain of HSV1 into the arm representations of M1 or PMv, or into area 46 or area 9 in the prefrontal cortex. Solid dots indicate the positions of neurons labeled by the retrograde transneuronal transport of virus. Labeled neurons are charted from two adjacent sections whose approximate anterior–posterior location is indicated at the bottom of each section. (Adapted from Zemanick *et al.*, 1991; Strick *et al.*, 1993; Middleton and Strick, 1994, 1997.)

and "PMv_{arm}"). Thus, the arm areas in M1 and PMv receive input from different portions of the dentate.

HSV1 injections into the FEF (Fig. 2) labeled neurons in the most caudal third of the dentate nucleus (see Lynch *et al.*, 1994). Prior studies have shown that this region of the dentate contains neurons that display changes in activity correlated with saccadic eye movements (e.g., van Kan *et al.*, 1993). This caudal portion of the dentate is strikingly different from the dentate regions that contained labeled neurons after virus injections into M1 and PMv (Fig. 6). The FEF is known to be an important component of the cortical system that controls voluntary eye movements in primates (for references and review, see Bruce and Goldberg, 1985; Bruce *et al.*, 1985). Thus, dentate projections to skeletomotor and oculomotor areas of cerebral cortex originate from separate regions of the nucleus.

B. Cerebellar Output to Prefrontal Cortex

Our initial studies on input to prefrontal cortex have focused on dorsolateral regions that are included in Walker's (1940) areas 9 and 46 (Fig. 2). These areas of prefrontal cortex have been reported to be involved in "working memory" and in the guidance of behavior based on transiently stored information rather than immediate external cues (e.g., Fuster, 1989; Funahashi *et al.*, 1989, 1993; Goldman-Rakic, 1990; Petrides, 1995). Areas 9 and 46 have both been shown to project to regions of the pontine nuclei (Leichnetz *et al.*, 1984; Glickstein *et al.*, 1985; Schmahmann and Pandya, 1995, 1997; Brodal, 1978) and to receive input from subdivisions of the ventrolateral thalamus (Kievit and Kuypers, 1977; Goldman-Rakic and Porrino, 1985; Barbas *et al.*, 1991; Yamamoto *et al.*, 1992; Middleton and Strick, 1994).

Virus injections into prefrontal cortex labeled many neurons in the dentate nucleus. These neurons were confined to the most ventral portions of the dentate and were concentrated rostrocaudally in the middle third of the nucleus (Fig. 6, "Area 46" and "Area 9"). Within this region of the dentate, neurons labeled after area 9 injections were found largely medial to neurons labeled after area 46 injections. These regions of the dentate clearly differ from the more dorsal regions of the nucleus that were labeled by virus injections in M1 or the PMv (Fig. 6) and the more caudal region of the dentate labeled by injections in the FEF.

Two main conclusions arise from these results. First, the output of the cerebellum can influence skeletomotor, oculomotor, and prefrontal regions of the cerebral cortex. Second, each of these different cortical regions receives input from a different region of the dentate. As a consequence, the dentate nucleus appears to contain a number of distinct "output channels," which project via the thalamus to specific areas of the cerebral cortex (Fig. 7).

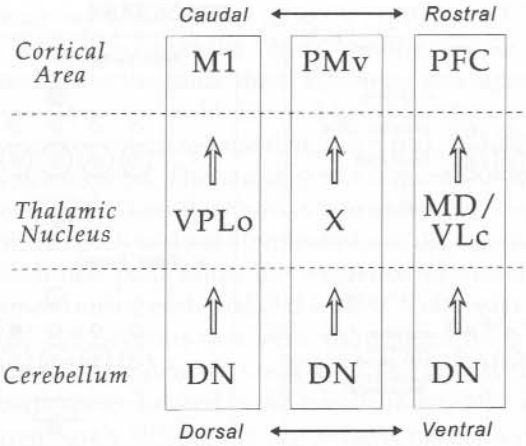

FIG. 7. Output channels in the dentate. Regions of the motor cortex (M1), premotor cortex (PMv), and prefrontal cortex (PFC) are each the target, via the thalamus, of projections from distinct regions of the dentate. The topographic trends in the localization of output channels related to these cortical areas are indicated at the top and bottom of the diagram.

III. Physiological Studies

A. Neuron Recording in Awake Trained Primates

The anatomical findings just described raise an important question. What is the nature of the information conveyed to the cerebral cortex by individual output channels? For example, do output channels that project to motor areas of cortex send signals related to the control of movement, while output channels directed to prefrontal cortex send signals related to some aspect of mnemonic behavior? To begin to address this issue we recorded the activity of single neurons in the dentate nucleus of awake monkeys trained to perform sequential pointing movements under two different task conditions (Mushiake and Strick, 1993, 1995). Briefly, in both conditions, the monkey faced a panel with five touch pads that were numbered 1 to 5 (left to right) (Fig. 8). A small red light-emitting diode (LED) was located over each touch pad. The monkey began a trial by placing his right hand on a hold key for a variable "Hold" period. In the *remembered sequence task* (REM task) (Fig. 8, left), LEDs over three touch

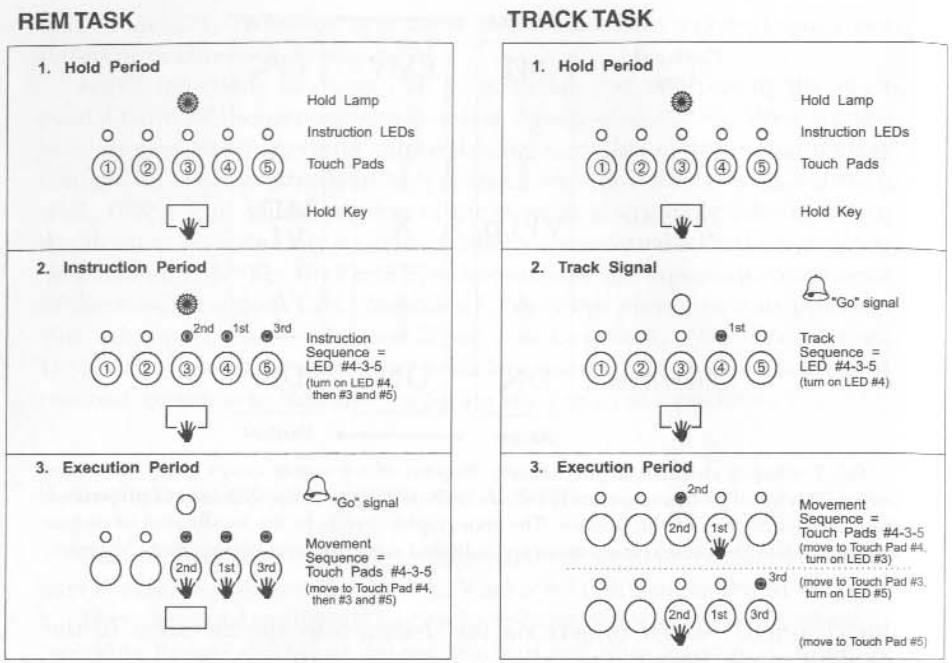

FIG. 8. REM and TRACK tasks. Monkeys faced a panel with five touch pads numbered 1 to 5. A small red LED was located over each touch pad (Instruction LEDs). The monkey began a trial by placing its right hand on a hold key in front of him for a "hold" period of 1.5–2.5 sec. Correct holding was signaled by a green LED (Hold Lamp) over the middle touch pad–LED combination. REM task: Instruction LEDs over three of the touch pads were illuminated in a sequence as an instruction to the monkey. At the end of a variable "Instruction" period of 1.5–2.5 sec, an auditory "Go" signal told the monkey to release the hold key and to press the three touch pads in the same order that the LEDs were illuminated. TRACK task: An instruction LED over a single touch pad was illuminated after a "Hold" period of 2.5–3.5 sec. The auditory "Go" signal was turned on at the same time. Following the onset of this signal, the monkey was required to release the hold key and press the indicated touch pad. As soon as the monkey contacted the first touch pad, an LED over a second touch pad was illuminated and the monkey was required to move to this touch pad. Then, when the monkey contacted the second touch pad, an LED over a third touch pad was illuminated and the monkey was required to move to this touch pad. (Adapted from Mushiake and Strick, 1993.)

pads were illuminated in a pseudorandom sequence as an instruction to the monkey. At the end of a variable "Instruction" period, an auditory "Go" signal told the monkey to release the hold key and press the three touch pads in the same order that they were illuminated. Thus, the sequence of movements that the monkey performed during each trial of the REM task was initially stored in "working memory" and then internally guided.

In the *tracking task* (TRACK task) (Fig. 8, right), an LED over a single touch pad was illuminated after the "Hold" period, and an auditory "Go" signal was turned on at the same time. Following this signal, the monkey was required to release the hold key and press the indicated touch pad. As soon as the monkey contacted the first touch pad, an LED over a second touch pad was illuminated. The monkey was required to quickly move to this second touch pad. When the monkey contacted the second touch pad, an LED over a third touch pad was illuminated and the monkey was required to move to this touch pad. Thus, the sequence of movements that the monkey performed during each trial of the TRACK task was externally cued.

We recorded 172 neurons that were task related during the reaction time (RT) period in the dentate nucleus of two trained monkeys. Most task-related neurons were located in the middle third of the dentate, rostrocaudally. Approximately 60% of the task-related neurons (102/172) were classified as *task independent*. These neurons displayed movement-related activity during the RT period of both REM and TRACK tasks. Most task-independent neurons were located dorsally in the dentate. This region is likely to be within the output channel that projects to M1 (see Figs. 6 and 7). Based on their firing patterns, it is likely that the neurons in this output channel are involved in defining the parameters of movements, independent of whether the movements are internally guided or externally cued.

However, approximately 40% of the task-related neurons in the dentate (70/172) were considered *task dependent* because their activity patterns differed substantially during TRACK and REM tasks. More than 75% of the task-dependent neurons (54/70) were termed *TRACK* neurons because they either displayed activity changes during the RT period only for the TRACK task or their changes in activity were more pronounced ($>\pm 50\%$) for the TRACK task than for the REM task. An example of a TRACK neuron is shown in Fig. 9. The rasters and averages are aligned on the hold key release. They illustrate the activity of this neuron during trials that began with a movement to touch pad 4 (4-5-3, 4-3-5, 4-3-1, 4-2-1). The individual trials in the rasters have been sorted according to the length of the RT period. This neuron displayed little or no modulation in its activity during the RT period of the REM task (Fig. 9, left). In contrast, the same neuron showed a clear increase in activity during the RT period of the TRACK task (Fig. 9, right).

Many of the TRACK neurons were located ventral and lateral to dentate neurons that were task related, but *task independent*. This localization suggests that TRACK neurons are within the output channel that innervates the PMv (see Figs. 6 and 7). Thus, the neurons in this output channel appear

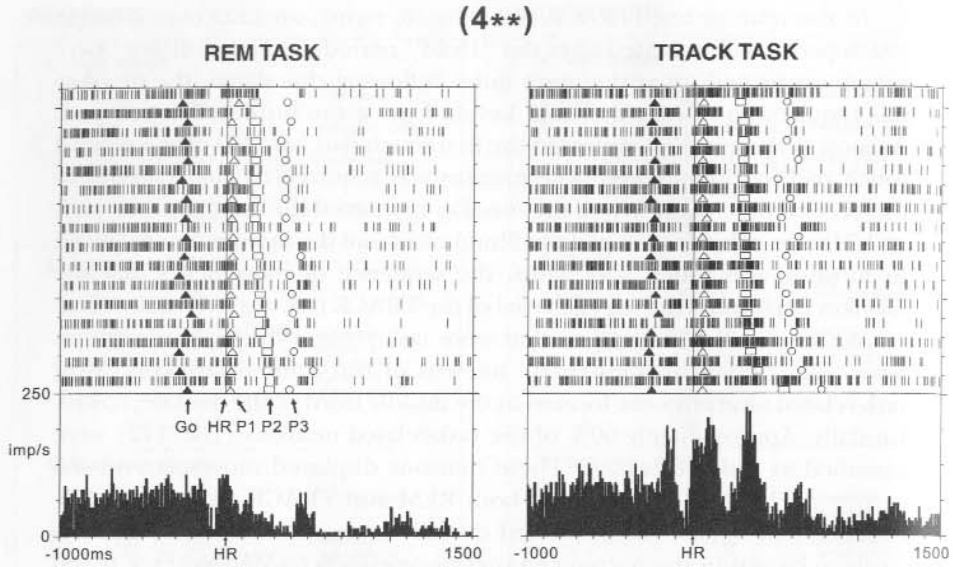

FIG. 9. Responses of a TRACK neuron in the dentate. The rasters and averages are aligned on the hold key release (HR). They illustrate the response of this neuron during trials that began with a movement to touch pad 4 (4**, i.e., 4-5-3, 4-3-5, 4-3-1, 4-2-1). The individual trials in the rasters have been sorted according to the length of the interval between the onset of the "Go" signal and HR (i.e., the RT period). Symbols indicate the onset of different behavioral events: filled triangle, "Go" signal; open triangle, press of the first touch pad in the sequence (P1); open square, press of the second touch pad (P2); open circle, press of the third touch pad (P3). Note that this neuron displayed a phasic increase in activity in the RT period only during the TRACK task. (Adapted from Mushiake and Strick, 1993.)

to be preferentially involved in the generation and control of sequential movements that are visually guided.

Approximately 16% (27/172) of the task-related neurons were *"instruction related"* (I-related), i.e., they displayed changes in activity during the instructed delay period (Fig. 10). Some of these I-related neurons displayed transient changes in activity immediately after the presentation of visual cues (Fig. 10, "Cue" neuron). Other I-related neurons displayed changes in activity only during the delay period following the illumination of the three instruction LEDs (Fig. 10, "Delay" neuron). Approximately one quarter of the I-related neurons (7/27) displayed "Delay" activity that depended on the sequence the animal was preparing to perform. Still other I-related neurons displayed two phases of activity during the instructed delay period (Fig. 10, "Cue + Delay" neuron). I-related neurons tended to be located in ventral regions of dentate. This site appears to be within

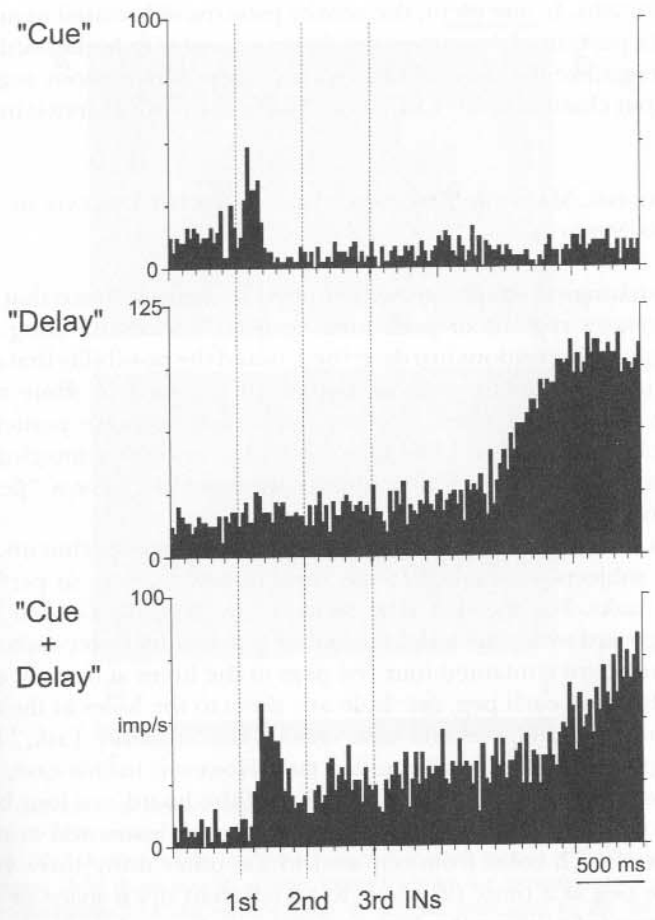

FIG. 10. Responses of I-related neurons in the dentate. The rasters and averages illustrate the activity of three different types of I-related neurons during the instructed delay period (first, second, and third INs). The trials are aligned on the presentation of the third instruction. The bin width for the averages is 20 msec. The trials illustrated all began with the illumination of LED #4. Note that some neurons displayed I-related activity after the presentation of a visual cue ("Cue" neuron, top), during the delay period following cue presentation ("Delay" neuron, middle), or during both the cue and delay periods ("Cue + Delay" neuron, bottom) (H. Mushiake and P. L. Strick, manuscript in preparation).

output channels that innervate prefrontal areas involved in working memory (areas 46 and 9, see Fig. 6). I-related neurons may also be within channels directed toward premotor areas concerned with motor preparation (e.g., the presupplementary motor area, see Wiesendanger and Wiesen-

danger, 1985b). In any event, the activity patterns of I-related neurons indicate that a portion of dentate output is concerned with higher-order motor and/or cognitive functions. Furthermore, these observations suggest that each output channel sends a unique signal to the cortical area it innervates.

B. Functional Magnetic Resonance Imaging of the Dentate in Human Subjects

The anatomical studies presented provide clear evidence that the dentate innervates regions of prefrontal cortex. This result, along with the physiological observations just described, raised the possibility that a portion of the output from the primate dentate is involved in some aspect of cognitive function. To test whether the human dentate participates in cognitive function, we used functional magnetic resonance imaging to study activation in the dentate while subjects attempted to solve a "pegboard" task (Kim *et al.*, 1994).

Seven healthy volunteers participated in these experiments. During imaging, subjects were asked to use their dominant limb to perform two different tasks. For the first task, termed the "Visually Guided Task," a small pegboard with nine holes was securely positioned over each subject's chest. The board contained four red pegs in the holes at its right end. The task was to move each peg, one hole at a time, to the holes at the opposite end of the board. The second task, termed the "Insanity Task," used the same pegboard as the visually guided task. However, in this case, four red pegs were placed in holes at the right end of the board *and* four blue pegs were placed in holes at the left end. Subjects were instructed to move the four pegs of each color from one end to the other using three rules: (1) move one peg at a time; (2) move to an adjacent open space or jump an adjacent peg (of a different color); and (3) move forwards, never backwards. No subject solved the insanity task during the period of scanning.

The major result of this study was that all seven of the subjects displayed a large bilateral activation in the dentate during attempts to solve the insanity task (Fig. 11B). Furthermore, in every subject, the extent of this activation was three to four times larger than that found during the visually guided task (Fig. 11A). In addition, the ventral portions of the dentate activated by the insanity task appeared to differ in their location from the portions of this nucleus activated during the visually guided task (Fig. 11). These results suggest two important conclusions. First, the cognitive demands associated with attempts to solve the insanity task lead to dentate activation. Second, the ventral regions of the dentate involved in cognitive processing are distinct from the dentate regions involved in the control of

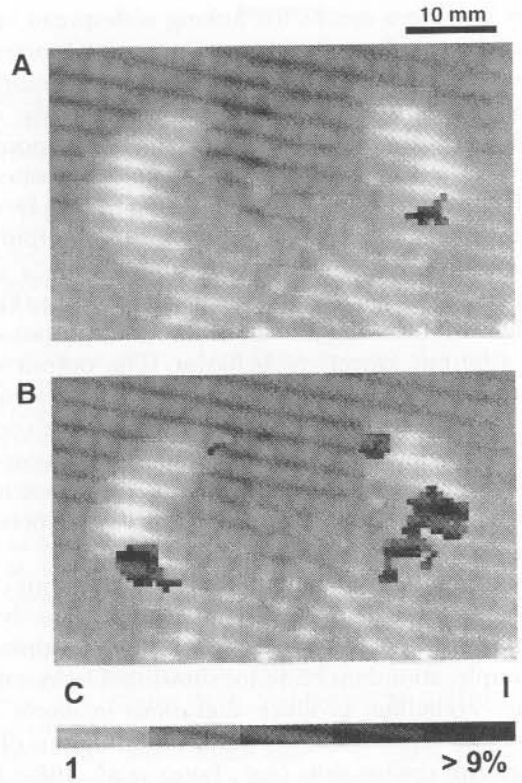

FIG. 11. Activation of dentate nucleus during cognitive processing. Maps of functional activation in the dentate for one subject during the visually guided task (**A**) and during the insanity task (**B**). Dentate nuclei are white crescent-shaped regions with low background signal intensity. Only those activation sites located within the dentate nuclei are shown. C, dentate contralateral to the moving limb; I, dentate ipsilateral to the moving limb; D, dorsal; V, ventral. (Adapted from Kim *et al.*, 1994.)

eye and limb movements, and are potentially within an output channel that innervates prefrontal cortex.

IV. Synthesis

The anatomical and physiological results just described represent a significant departure from prior theories about the functional organization of cerebellar loops with the cerebral cortex. The classical view of these

loops is that they provide a means for linking widespread regions of the cerebral cortex, such as prefrontal and posterior parietal cortex, with motor output at the level of the primary motor cortex (e.g., Kemp and Powell, 1971). Our results support an alternative view. Cerebellar output gains access to multiple cortical areas. These areas include regions involved in cognitive function, as well as those involved in the control of movement. In addition, we have proposed that the clustering of output neurons that project to an individual cortical area creates distinct output channels in the dentate. The output channels related to motor areas appear to be separate from those associated with the prefrontal cortex (Figs. 6 and 7).

Our physiological results suggest that individual output channels are concerned with different aspects of behavior. The output channel that projects to M1 may be involved in the control of specific movement parameters. The output channel that innervates the PMv may be concerned with higher order aspects of motor behavior such as the generation of sequential movements based on external cues. Output channels that influence the prefrontal cortex may be involved in cognitive aspects of behavior such as working memory.

Given the topographic organization of individual output channels and our physiological results, it is not hard to imagine that dysfunction of different regions within the dentate would lead to distinct changes in behavior. For example, abundant evidence shows that lesions of sensorimotor regions of the cerebellum produce alterations in motor behavior. In contrast, there are also reports that lesions of other regions of the cerebellum result in cognitive dysfunction (e.g., Botez *et al.*, 1989; Leiner *et al.*, 1991, 1993; Schmahmann, 1991; Ivry and Keele, 1989; Fiez *et al.*, 1992; Petersen and Fiez, 1993; Canavan *et al.*, 1994).

At this point, the full extent of cerebellar influence on the cerebral cortex remains to be determined. One of the immediate goals of our present research is to resolve this question. The outcome of these studies should have an important impact on concepts regarding cerebellar contributions to behavior and provide additional insights into the consequences of cerebellar dysfunction.

Acknowledgments

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THE CEREBELLAR–HYPOTHALAMIC AXIS: BASIC CIRCUITS AND CLINICAL OBSERVATIONS

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Experimental studies on a variety of mammals, including primates, have revealed direct and reciprocal connections between the hypothalamus and the cerebellum. Although widespread areas of the hypothalamus project to cerebellum, axons arise primarily from cells in the lateral, posterior, and dorsal hypothalamic areas; the supramammillary, tuberomammillary, and lateral mammillary nuclei; the dorsomedial and ventromedial nuclei; and the periventricular zone. Available evidence suggests that hypothalamocerebellar cortical fibers may terminate in relation to neurons in all layers of the cerebellar cortex. Cerebellohypothalamic axons arise from neurons of all four cerebellar nuclei, pass through the superior cerebellar peduncle, cross in its decussation, and enter the hypothalamus. Some axons recross the midline in caudal areas of the hypothalamus. These fibers terminate primarily in lateral, posterior, and dorsal hypothalamic areas and in the dorsomedial and paraventricular nuclei. Evidence of a cerebellar influence on the visceromotor system is presented in two patients with vascular lesions: one with a small defect in the medial cerebellar nucleus and the other with a larger area of damage involving primarily the globose and emboliform nuclei. Both patients exhibited an abnormal visceromotor response. The second, especially, showed abnormal viscero-

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