



# Tyrosine Hydroxylase- and Dopamine Transporter-Immunoreactive Axons in the Primate Cerebellum

## Evidence for a Lobular- and Laminar-Specific Dopamine Innervation

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The cerebellum seems to play a critical role in many motor and cognitive functions, including those that are disturbed in schizophrenia. Although dopamine is known to influence the motor or cognitive functions mediated by other brain regions and to play a role in the pathophysiology of schizophrenia, the cerebellum has not been thought to be a target of dopamine-containing axons. However, given recent reports of dopamine receptors in the cerebellum, we sought to determine whether axons immunoreactive for the proteins involved in dopamine synthesis and reuptake are present in the cerebellum of macaque monkeys. We found that axons immunoreactive for the dopamine membrane transporter, a specific marker of dopamine axons, were present in high density, but only in certain lobules of the cerebellar vermis. In addition, these axons were found

principally in the granule cell layer, where they densely arborized immediately subjacent to the Purkinje cells. Similarly, axons labeled for tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis, were also present in high density in the granule cell layer of the same lobules of the vermis. In contrast, axons immunoreactive for dopamine beta-hydroxylase, a marker of noradrenergic axons, exhibited a different and more widespread pattern of innervation. These findings are consistent with a dopamine innervation of the primate cerebellum that is both lobular- and laminar-specific, and they suggest that dopamine may play a role in certain cerebellar functions.

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The primary function of the cerebellum has traditionally been considered to involve the control and integra-

tion of motor processes, including the coordination of goal-directed movements and the regulation of posture (Ito 1984). However, recent evidence suggests that the cerebellum may also be important in cognitive functions (Schmahmann 1991; Kim et al. 1994). For example, neuro-imaging studies have demonstrated activation in the cerebellum during word-association tasks (Petersen and Fiez 1993), as well as during mental imagery and mental counting (Ryding et al. 1993). These cognitive aspects of the cerebellum seem to involve the lateral hemispheres and the dentate nucleus (Schmahmann 1991; Petersen and Fiez 1993; Kim et al. 1994). In con-

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trast, the medial regions of the cerebellum, such as the vermis and fastigial nucleus, are primarily associated with motor control of the trunk and head, including smooth pursuit eye movements (Ito 1984).

The cerebellum has also been implicated as a site of dysfunction in schizophrenia, a disorder characterized by certain types of motor and cognitive impairments. For example, many subjects with schizophrenia exhibit abnormalities in smooth pursuit eye movements (Holzman et al. 1973; Levy et al. 1994; Hutton and Kennard 1998). In addition, some of the cognitive deficits observed in individuals with schizophrenia, such as impairments in planning, verbal fluency, abstract thinking, and working memory, are present in patients with cerebellar lesions (Schmahmann and Sherman 1998). Furthermore, studies of schizophrenic subjects have revealed reductions in cerebellar volume (Jacobsen et al. 1997; Weinberger et al. 1980), metabolism (Volkow et al. 1992), and blood flow (Steinberg et al. 1995), especially in the vermal regions. Consistent with these observations, the size of Purkinje cells has been reported to be decreased in the vermis of subjects with schizophrenia (Tran et al. 1998).

Abnormalities in dopamine (DA) neurotransmission have long been considered to be involved in the pathophysiology of schizophrenia (Carlsson et al. 1997; Davis et al. 1991; Grace 1991; Snyder 1972), and DA is known to play a critical role in the regulation of motor and cognitive functions in both cortical and subcortical structures (Goldman-Rakic 1998; Lewis and Sesack 1997). However, whether DA directly influences motor or cognitive functions at the level of the cerebellum is unclear. Historically, the cerebellum was not thought to utilize DA as a neurotransmitter, and the DA present in the cerebellum was considered to serve only as a precursor for noradrenaline. More recently, biochemical studies have demonstrated DA release and binding (Chrapusta et al. 1994; Panagopoulos et al. 1991), and the presence of DA receptors (Diaz et al. 1995; Khan et al. 1998), in the rodent cerebellum. However, it is unclear whether these findings can be generalized to the primate cerebellum, given the marked differences between rodents and primates in the organization of other DA projection systems (Berger et al. 1991; Lewis and Sesack 1997). In addition, the presence of DA axons in the cerebellum has not been definitively shown in any species. Consequently, in this study, we used immunocytochemical techniques to address the following questions. First, does the cerebellum of macaque monkeys contain axons immunoreactive for tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine synthesis, and for the DA membrane transporter (DAT), a specific marker of DA axons (Ciliax et al. 1995; Freed et al. 1995; Lewis and Sesack 1997; Sesack et al. 1998)? Second, if so, do the distributions of TH- and DAT-positive axons differ from that of axons immunoreactive for

dopamine- $\beta$ -hydroxylase (DBH), the synthesizing enzyme for noradrenaline? Third, do TH- and DAT-labeled axons have a distinctive lobular or laminar distribution that may provide insight into the role of DA in the motor and/or cognitive functions of the cerebellum?

## MATERIALS AND METHODS

### Tissue Preparation

Five young adult, male cynomolgus (*Macaca fascicularis*) monkeys were used in this study. Animals were deeply anesthetized (ketamine 25 mg/kg and pentobarbital 30 mg/kg) and then perfused transcardially with cold 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4), as previously described (Noack and Lewis 1989). Brains were then immediately removed, cut into 5–6 mm thick coronal or sagittal blocks, and immersed in 4% paraformaldehyde for 2 or 6 hours. Tissue blocks were washed in a series of graded sucrose solutions and sectioned (40  $\mu$ m) on a cryostat.

### Immunocytochemistry

Free-floating sections were incubated for 30 min at room temperature in phosphate buffered saline (PBS), pH 7.4, containing 0.3% Triton X-100 and 4.5% normal donkey serum (NDS; Jackson ImmunoResearch, West Grove, PA). Sections were then incubated at 4°C for 40–48 hours in PBS containing 0.3% Triton X-100, 3% NDS, 0.5 mg/ml bovine serum albumin and a monoclonal mouse TH antibody (diluted 1:10,000; kindly provided by Dr. Greg Kapatos, Wayne State University), a monoclonal rat DAT antibody (diluted 1:2,000; Chemicon, Temecula CA), or a polyclonal rabbit DBH antibody (diluted 1:10,000; Eugene Tech, Ridgefield Park, NJ). The specificity of these antibodies has been demonstrated previously by immunoprecipitation, Western blot, and immunocytochemical studies in primate brain (Akil and Lewis 1993; Lewis et al. 1993, 1994, 1998; Miller et al. 1997; Wolf et al. 1991).

Sections were incubated for 1 hour at room temperature in PBS containing 3% NDS, 0.3% Triton X-100, and biotinylated donkey anti-mouse, anti-rat, or anti-rabbit IgG (1:200; Jackson), and then processed with the avidin-biotin method of Hsu et al. (1981), using an Elite Vectastain ABC kit (Vector Laboratories, Burlingame, CA) and 3, 3'-diaminobenzidine (DAB). Following the DAB reaction, tissue sections were mounted on gel-coated slides, and the reaction product was intensified with serial immersions in aqueous solutions of silver nitrate and gold chloride, as previously described (Pucak et al. 1996). Cerebellar lobules and folia were identified using published criteria (Madigan and Carpenter 1971).

## RESULTS

### Distribution of TH-Labeled Axons

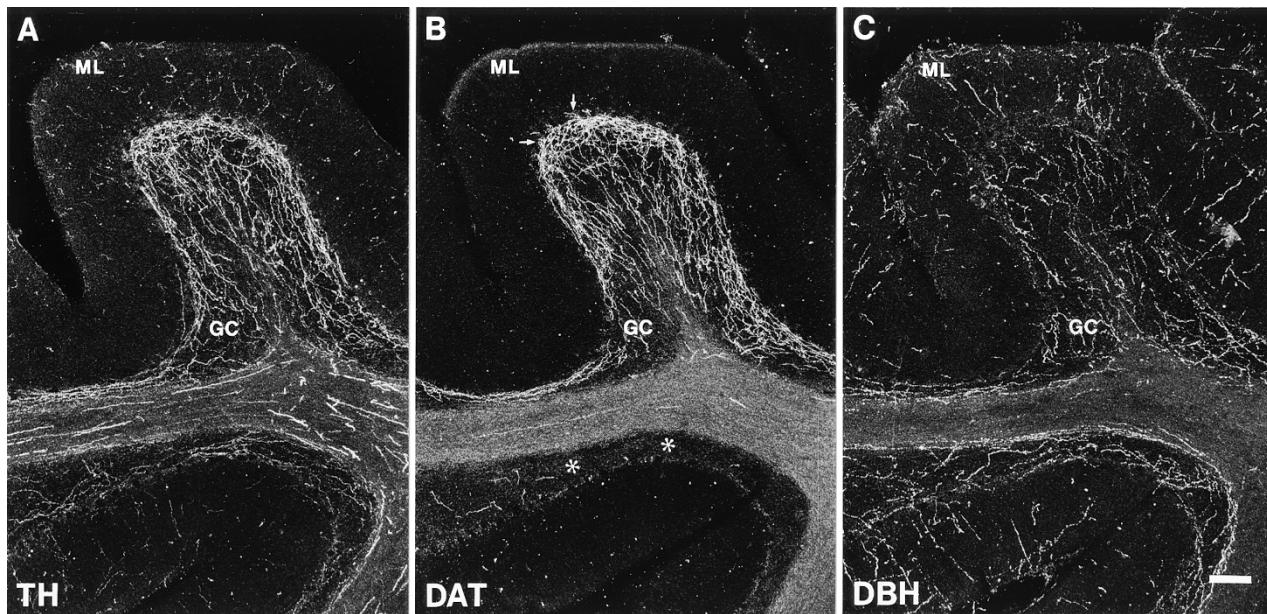
In each of the five monkeys examined, axons labeled by the TH antibody were present in low density throughout the cerebellar hemispheres and vermis. In addition, TH-immunoreactive (IR) axons were generally located in all three layers of the cerebellar cortex. However, within certain lobules of the cerebellar vermis, the granule cell layer contained a very high density of TH-IR axons (Fig. 1A). The labeled fibers formed a particularly dense plexus immediately below the Purkinje cell layer, with some axons extending into that layer. TH-IR axons were also found in the molecular layer, but their density was substantially lower than in the granule cell layer.

### Distribution of DAT-Labeled Axons

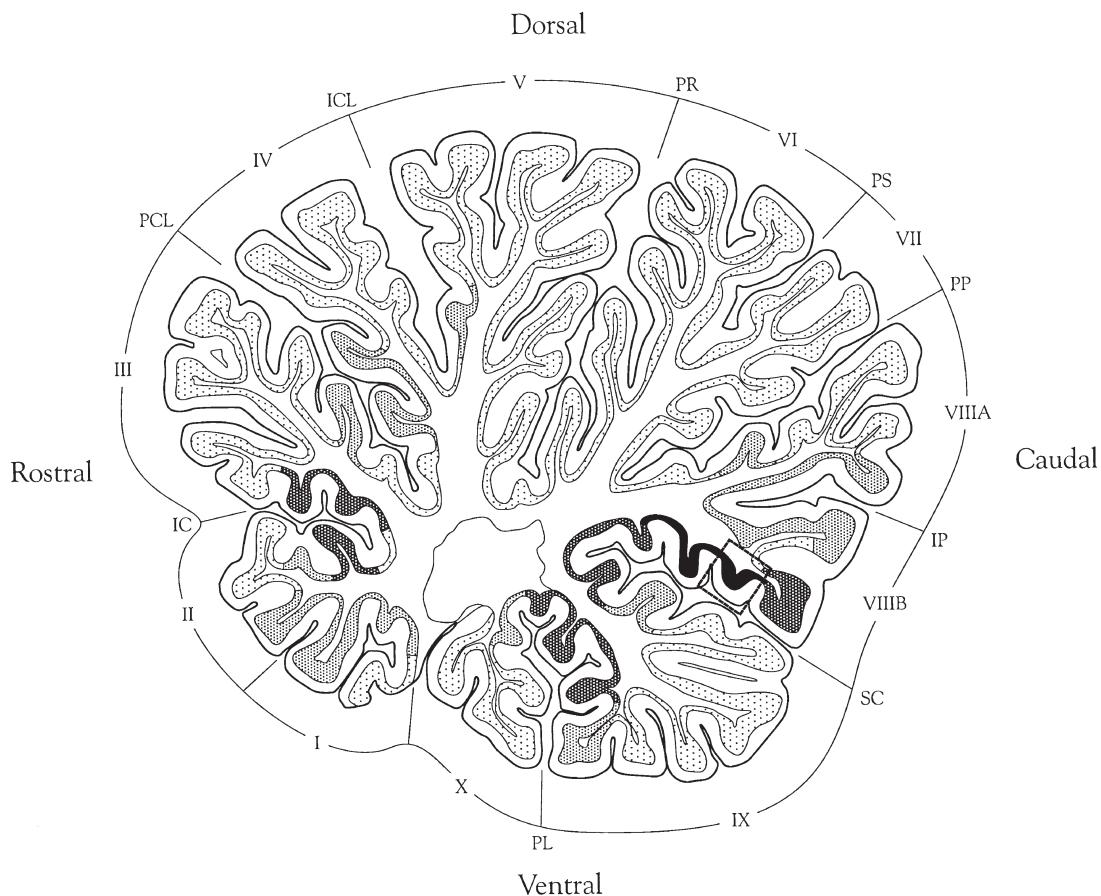
Because TH is expressed in all catecholamine-synthesizing neurons, we also evaluated the distribution of axons immunoreactive for DAT, a protein found only in DA neurons (Ciliax et al. 1995; Freed et al. 1995; Lewis and Sesack 1997; Sesack et al. 1998). In all animals examined, axons labeled by the DAT antibody were present only in the cerebellar vermis (Fig. 1B), and not in the cerebellar hemispheres. Furthermore, within the vermis, labeled axons were present only in portions of a

subset of lobules (Fig. 2). In lobules II, III, and IV, DAT-IR axons were found primarily in the depths of the intracentral and preculminate fissures and to a lesser extent in the more external folia of these lobules. In lobules VIIIA and VIIIB, DAT-IR axons were present in both the external and internal folia, although the density of immunoreactive axons was greater in the internal folia. Within lobules IX and X, DAT-IR axons were also present in the folia of the posterolateral fissure. In contrast, DAT-positive fibers were never found in lobules V–VII. Finally, the relative density of DAT-IR axons also differed substantially within some lobules. For example, a particularly high density of DAT-IR axons was consistently found in the dorsal bank of the secondary fissure in lobule VIIIB; whereas, very few labeled axons were evident in the folium directly across the white matter (Fig. 1B). These lobular patterns of DAT-IR axons precisely paralleled the distribution of the areas of high density of TH-IR axons.

In every lobule that contained DAT-IR axons, labeled processes were found primarily in the granule cell layer (Fig. 1B). Labeled axons were distributed throughout this layer, with a particularly dense plexus of fibers immediately beneath the Purkinje cell layer, a pattern virtually identical to that of TH-IR axons. Some axons extended into the Purkinje cell layer, where they coursed between and around unlabeled cell bodies (Fig. 3). In contrast to the distribution of TH-IR axons, DAT-IR ax-



**Figure 1.** Darkfield photomicrographs of TH-IR (A), DAT-IR (B) and DBH-IR (C) axons in adjacent sections through vermal lobule VIIIB of monkey cerebellum (see Fig. 2 for illustration of location). Note that both the TH- and DAT-IR axons are primarily restricted to the granule cell layer (GC), with some clusters of axons (arrows in B) extending into the Purkinje cell layer. TH-IR axons are also present in the molecular layer (ML), but no DAT-IR axons are detectable in this layer. In contrast, DBH-IR axons (C) are distributed across all layers. In addition, the restricted lobular distribution of the DAT-IR axons is illustrated by the marked paucity of these axons in the granule cell layer (asterisks in B) of the folium across the white matter; whereas, the density of DBH-IR axons does not seem to differ across lobules. Scale bar = 150  $\mu$ m.



**Figure 2.** Schematic drawing of a sagittal section through the vermis of monkey cerebellum illustrating the relative density of DAT-IR axons. The relative density of DAT-IR axons in the granule cell layer (shaded area) is illustrated by the density of dots (e.g. lowest density of dots indicates no DAT-IR axons, while solid black denotes a high density of DAT-IR axons). Bold lines indicate divisions between lobules, which are labeled with roman numerals. In most instances, these lines also indicate vermal fissures. IC = intracentral fissure, ICL = intraculminate fissure, IP = intrapyramidal fissure, PCL = preculminate fissure, PL = posterolateral fissure, PP = prepyramidal fissure, PR = primary fissure, PS = posterior superior fissure, SC = secondary fissure. The dashed box indicates the approximate location of the photomicrographs shown in Figure 1.

ons were never found in the molecular layer (compare Figs. 1A and 1B).

#### Distribution of DBH-Labeled Axons

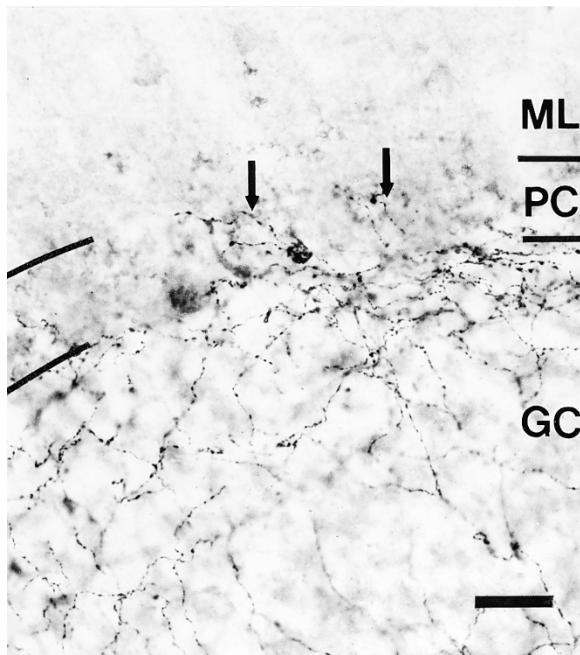
To compare the distribution patterns of TH- and DAT-IR axons to the noradrenergic innervation of the monkey cerebellum, we conducted a similar analysis of axons immunoreactive for DBH. Consistent with previous reports (Hökfelt and Fuxe 1969), DBH-IR fibers were present in all lobules of the cerebellar hemispheres and vermis, although some differences in the density of labeled axons were apparent across lobules. Labeled axons were distributed in all three layers without a clear predominance in any layer (Fig. 1C).

In most locations, DBH-IR and TH-IR axons had similar patterns of distribution, although the number of DBH-labeled axons, and their intensity of immunoreactivity, always exceeded that of TH-IR axons (compare

the molecular layer in Figs. 1A and 1C). In contrast, in the locations where DAT-IR axons were present, the density of TH-IR axons far exceeded that of DBH-IR axons (compare the granule cell layer across the panels of Fig. 1).

#### DISCUSSION

The present study demonstrates the existence of a lobular- and laminar-specific distribution of DAT-IR axons in the cerebellar vermis of macaque monkeys. The principal function of DAT is to remove DA from the extracellular space, terminating its action at postsynaptic receptors. Indeed, recent studies suggest that DAT is the critical element regulating the actions of DA (Jaber et al. 1997; Kuhar 1998). Thus, DAT immunoreactivity would be expected to label DA-containing axons selectively, a view supported by multiple lines of evidence in other



**Figure 3.** Brightfield photomicrograph illustrating the distribution of DAT-IR axons in the granule cell layer (GC), molecular layer (ML), and Purkinje cell layer (PC) of the monkey cerebellar vermis. Note that labeled axons are present in the GC with a plexus of labeled axons immediately beneath the PC. Some labeled axons (arrows) extend into the PC. Also note that the ML is devoid of DAT-IR axons. Scale bar = 30 Fm.

brain regions of both rodents and primates (Ciliax et al. 1995, 1999; Freed et al. 1995; Lewis and Sesack 1997; Sesack et al. 1998). For example, the DAT antibody used in this study robustly labels the DA-containing neurons of the primate mesencephalon, but does not label any neurons that utilize other monoamines (Ciliax et al. 1999; Lewis and Sesack 1997). Thus, the findings of the present study provide evidence for a restricted DA innervation of the primate cerebellum.

This interpretation is supported by several convergent findings. First, axons immunoreactive for TH showed patterns of distribution that were quite similar to that of DAT-IR axons (compare Figs. 1A and 1B). These comparisons strongly suggest that some regions of the cerebellar vermis are innervated by axons that contain both the synthesizing and reuptake proteins for DA. However, the distribution of TH-labeled axons was more extensive than that of DAT-IR axons, suggesting that the TH antibody was also recognizing noradrenergic axons. Indeed, the distribution of TH-IR axons seems to be a composite of the distributions of DBH-IR and DAT-IR axons, although the density of TH-IR axons was always lower than that of DBH-IR axons in locations, such as the molecular layer, that lacked DAT immunoreactivity (see Fig. 1). These differences are consistent with an extensive series of studies in the

monkey cerebral cortex demonstrating that TH antibodies labeled only a small subpopulation of DBH-IR axons (Noack and Lewis 1989; Akil and Lewis 1993) but over 95% of DAT-IR axons (Lewis et al. 1998). However, it is possible that the distribution of DA axons in the primate cerebellum is more extensive than revealed by the distribution of DAT-IR axons, because, at least in rodent frontal cortex, some DA axons seem to contain low or nondetectable levels of DAT (Sesack et al. 1998).

Second, the interpretation that these DAT-IR axons are dopaminergic is supported by recent studies on the distribution of DA receptors in the cerebellum. For example, Khan et al. (1998), used subtype-selective antibodies to demonstrate that D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> DA receptors are expressed by Purkinje cells in rodent and human cerebella. In addition, the mRNA for the D<sub>3</sub> receptor seems to be localized to Purkinje cells in lobules IX and X of rodent cerebellum (Diaz et al. 1995). These similarities in the distributions of pre- and postsynaptic DA markers support an anatomically restricted, but functionally significant, dopaminergic innervation of the primate cerebellum.

Third, although early investigations did not reveal projections from any of the DA-containing cell groups to the cerebellum (Lindvall and Björklund 1978), a recent study in the rat demonstrated a projection from the ventral tegmental area to the cerebellar cortex (Ikai et al. 1992). Furthermore, this projection was shown to be immunoreactive for TH, and to terminate only in the granule and Purkinje cell layers. However, similar transport studies in the monkey are required to confirm that such a projection pathway is the source of the DAT-IR and TH-IR axons observed in the present study. Thus, although additional investigations are required to confirm unequivocally the existence of a restricted DA innervation of the primate cerebellum, the available data are consistent with this interpretation.

The presence of a DA innervation of the primate cerebellum is of potential importance for the interpretation of neuroimaging studies that have examined DA systems in other brain regions by employing ratios referenced to the cerebellum (Hume et al. 1996; Kapur et al. 1997; Nyberg et al. 1996; Vallabhajosula et al. 1997; Wang et al. 1996). Although the presence of a DA innervation in the cerebellum may represent a confound for this approach, the highly restricted distribution of DA axons to the cerebellar vermis, in concert with their relatively low density compared to such structures as the striatum, may render this concern more apparent than real.

Andreasen et al. (1996) hypothesize that disturbances in the circuitry linking the cerebellum, thalamus, and prefrontal cortex contribute to many of the abnormalities in cognition that are characteristic of schizophrenia. Although connections among these brain regions are clearly present in the primate brain

(Middleton and Strick 1994), this circuitry involves the cerebellar hemispheres and dentate nucleus, and not the vermis. Thus, although DA is known to play a critical role in cognitive functions mediated by other brain regions, such as the prefrontal cortex (Brozoski et al. 1979; Sawaguchi et al. 1988; Sawaguchi and Goldman-Rakic 1991), the results of the present study suggest that DA is unlikely to have an influence on cognitive processing at the level of the cerebellum. However, the cerebellar vermis does play a role in certain motor functions (Ito 1984). Interestingly, individuals with schizophrenia have long been recognized to exhibit a variety of disturbances in motor control. For example, numerous studies have demonstrated that schizophrenic subjects display abnormalities in smooth pursuit eye movements (Holzman et al. 1973; Hutton and Kennard 1998; Levy et al. 1994). The fastigial nucleus, the principal target of efferents from the cerebellar vermis (Ito 1984), is activated during pursuit eye movements (Fuchs et al. 1993; Vilis and Hore 1981). Thus, the DA innervation of the primate cerebellar vermis described in the present report may reveal a new locus of action for DA in the pathophysiology of schizophrenia.

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