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# Distribution of Dopamine $D_2$-Like Receptors in the Human Thalamus: Autoradiographic and PET Studies

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The distribution of dopamine (DA) $D_2$-like receptors in the human thalamus was studied using *in vitro* autoradiographic techniques and *in vivo* positron emission tomography in normal control subjects. [$^{125}$I]Epidepride, which binds with high affinity to DA $D_2$ and $D_3$ receptors, was used in autoradiographic studies to determine the distribution and density of $D_2$-like receptors, and the epidepride analogue [$^{18}$F]fallypride positron was used for positron emission tomography studies to delineate $D_2$-like receptors *in vivo*. Both approaches revealed a heterogeneous distribution of thalamic $D_{2/3}$ receptors, with relatively high densities in the intralaminar and midline thalamic nuclei, including the paraventricular, parataenial, paracentral, centrolateral, and centromedian/parafascicular nuclei. Moderate densities of $D_{2/3}$ sites were seen in the mediodorsal and anterior nuclei, while other thalamic nuclei expressed lower levels of $D_2$-like receptors. Most thalamic nuclei that express high densities of $D_2$-like receptors project to forebrain DA terminal fields, suggesting that both the thalamic neurons expressing $D_2$-like receptors and the projection targets of these neurons are regulated by DA. Because the midline/intralaminar nuclei receive prominent projections from both the ascending reticular activating core and the hypothalamus, these thalamic nuclei may integrate activity conveying both interoceptive and exteroceptive information to telencephalic DA systems involved in reward and cognition.

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## INTRODUCTION

The midline and intralaminar nuclei of the thalamus have historically been considered to be part of the nonspecific thalamus, a diencephalic way-station of the 'ascending reticular activating system' (Jasper, 1949). However, contemporary studies have revealed that the projections of neurons within the midline/intralaminar complex are specific for distinct forebrain targets (Berendse and Groenewegen, 1990, 1991; Moga *et al*, 1995; Turner and Herkenham, 1991), and have challenged the concept of 'nonspecificity' of these nuclei (Groenewegen and Berendse, 1994). The midline/intralaminar nuclei have figured prominently both in recent post-mortem and imaging studies and in theoretical considerations of the pathophysiology of schizophrenia (Andreasen, 1997; Buchsbaum *et al*, 1996; Byne *et al*, 2002; Cohen and Yurgelun-Todd, 2001; Deutch *et al*, 1995; Popken *et al*, 2000) addictive disorders (Staley and Mash, 1996; Volkow *et al*, 1996, 1997; Wang *et al*, 1997; Yousef *et al*, 1995), and Parkinson's disease (PD) (Feigin *et al*, 2002; Filion, 2000; Freeman *et al*, 2001; Henderson *et al*, 2000; Hershey *et al*, 1998; Kaasinen *et al*, 2000).

There have been few studies of thalamic dopamine (DA) function in humans, and relatively little is known of the organization and distribution of dopaminergic axons and receptors in the human thalamus. We and others, using both binding studies in post-mortem tissue and *in vivo* radiolabeling approaches, have previously reported that $D_2$-like DA receptors are present in the human thalamus in moderately high density (Delforge *et al*, 2001; Farde *et al*, 1997; Gurevich and Joyce, 1999; Hagelberg *et al*, 2002; Hall *et al*, 1996a; Halldin *et al*, 1995; Kessler *et al*, 1993b, 1997; Mukherjee *et al*, 2001; Wang *et al*, 1997). However, extant studies have typically examined DA receptors of the thalamus as part of more global analyses of extrastriatal DA systems, and there are almost no focused studies on the intra-thalamic distributions of $D_2$-like receptors using both autoradiographic and *in vivo* imaging approaches. We therefore assessed the regional distribution of DA $D_2$-like receptors in the human thalamus both *in vitro* and *in vivo*, as revealed with epidepride analogues that bind with high affinities to $D_{2/3}$ receptors.

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## METHODS

### Autoradiographic Studies

Brains were obtained from three male subjects (ages 43, 55, and 60 years) who were free of neurological and psychiatric disease and were not maintained on any psychotropic medications. The subjects all died in the hospital, two of acute cardiac events and the other from a pulmonary embolism; in all cases the post-mortem intervals were less than 6 h. In no subject was there a previous history of neurological or psychiatric illnesses. The brains were examined for gross structural abnormalities and then divided along the mid-sagittal plane, with one hemisphere being stored in 10% formalin and the other frozen and stored at $-80^{\circ}$C. Coronal sections from the fixed hemisphere were prepared and stained conventionally to determine if any neuropathological changes were present; none were noted. The frozen hemisphere was slowly thawed to $-20^{\circ}$C and then cut coronally into tissue blocks 1–2 cm thick, from which 30 μm frozen sections were cut. The slide-mounted sections were stored at $-20^{\circ}$C.

Autoradiographic methods using [$^{125}$I]epidepride were used to determine the densities of $D_2$-like-binding sites. The sections were preincubated at room temperature for 30 min in 50 mM Tris-HCl (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgSO_4$, 1 mM EDTA, and 100 μM ascorbate. The tissue was then incubated in Tris buffer containing 50 pM [$^{125}$I]epidepride for 3 h at room temperature. Sections were exposed to HyperB film (Amersham) for 2–6 days, and from these camera lucida drawings were made through the thalamus; nuclear boundaries were defined as shown in the atlas of Mai *et al* (1997).

In order to assess basal ganglia $D_2$-like binding the sections were apposed to film for 2 days. Due to the markedly different densities of DA receptors in the basal ganglia and thalamus, sections through the thalamus were subsequently exposed to film for 7 days. Linearity was assessed by comparing optical densities with brain paste standards containing known levels of radioactivity; these standards were coexposed with the brain sections. All thalamic nuclei were within the linear range of optical densities at the 7-day exposure time.

The densities of $D_{2/3}$-binding sites were determined by computer-assisted densitometry using NIH Image 1.6 (developed at the US National Institutes of Health and available on the internet at http://rsb.info.nih.gov/nih-image). Standards containing varying concentrations of $^{125}$I in homogenized brain tissue were used to generate $B_{max}$ values, based on a $K_D$ of 24 pM for epidepride. Regions of interest were defined and outlined with reference to the nuclei defined in the atlas of Mai *et al* (1997).

### *In Vivo* PET Imaging

Positron emission tomographic imaging was performed in five normal subjects (three males and two females, ages 21–45 years) who were free of documented neuropsychiatric illnesses and use of psychoactive medications. All subjects had a complete physical examination, including a neurological examination. In addition, neuropsychological tests to assess cognitive function and urinary drug screens were performed. The studies were conducted in accord with the guidelines of the Declaration of Helsinki and were approved and overseen by the Vanderbilt University Institutional Review Board.

PET scans were performed using a General Electric Advance PET scanner in the 3-D mode; this unit has an in-plane and axial resolution of 4.5–5.5 mm. Subjects were positioned on the scanner bed and 4.5–5.0 mCi of the epidepride analogue [$^{18}$F]fallypride (specific activity $>2000$ Ci/mmol) was administered intravenously; serial emission scans were then obtained for up to 240 min. A measured attenuation correction was performed, and regional binding potentials determined using the reference region method (Lammertsma *et al*, 1996). MRI scans of the brain were performed using thin section inversion prepared T1-weighted gradient echo sequences (IR SPGR, TE = 3.6, TR = 19, TI = 400, 24 cu field of view) in the sagittal (slice thickness 1.2–1.3 mm) and coronal (slice thickness 1.4–1.5 mm) planes. In addition, fast spin echo axial spin density weighted (TE = 19, TR = 5000, 3 mm thick) and T2-weighted (TE = 106, TR = 5000, 3 mm thick) slices were obtained to exclude any structural abnormalities. The PET scans were coregistered with each other and the thin section IR SPGR MRI scans using a mutual information rigid body

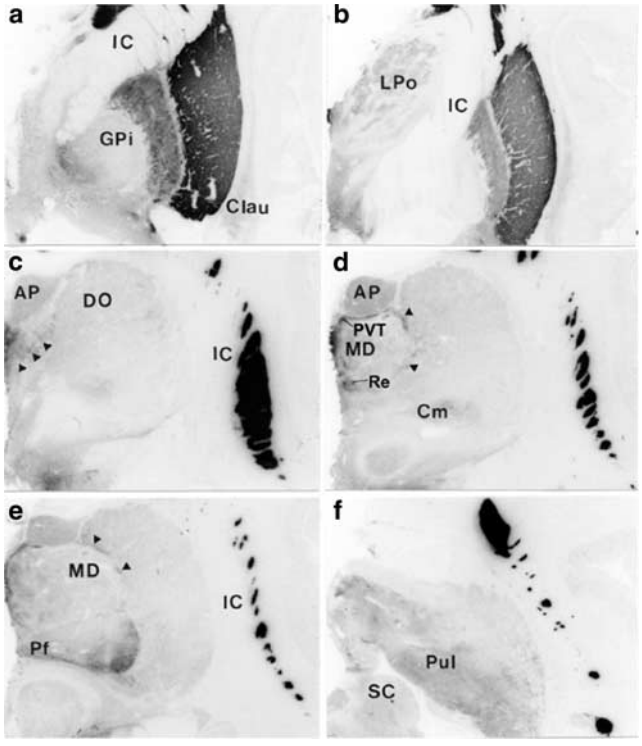


**Figure 1** Low power photomicrographs demonstrating the heterogeneous pattern of [$^{125}$I]epidepride labeling in the thalamus. Images are from coronal sections in rostral (a) to caudal (d) order. (a and b) In the rostral thalamus the density of [$^{125}$I]epidepride binding is relatively low, the exception being in the lateroposterior nucleus (LPo). More caudally (c) and (d), relatively dense [$^{125}$I]epidepride binding can be clearly seen in the intralaminar nuclei, particularly in the midline PVT and the paracentral nuclei. Strong binding in the centrolateral nucleus (arrowheads in c) and the medial aspects of the mediodorsal nucleus (MD, in panels d and e) can also be observed, as can moderately dense binding in the centrolateral nucleus (Cm in panel d). A moderate density of binding sites can also be seen in the principle anterior nucleus (AP). In the caudal thalamus (f) low-to-moderate [$^{125}$I]epidepride binding within the pulvinar is present.

registration (Maes *et al*, 1997). Regions of interest were outlined on the MRI scans and automatically transferred to the serial PET scans.

## RESULTS

### *In Vitro* Autoradiography

[$^{125}$I]Epidepride binding revealed a heterogeneous distribution of $D_{2/3}$ receptors in the human thalamus (see Figures 1 and 2; Table 1). The distribution of thalamic [$^{125}$I]epidepride binding largely conformed to recognized nuclear boundaries, with the most dense labeling seen in the anterior midline group, including the paraventricular (PVT) and parataenial (PT) nuclei (Figure 1 and Table 1). The density of $D_{2/3}$-binding sites in this region was roughly comparable to that seen in the substantia nigra (see Table 1).

Relatively dense [$^{125}$I]epidepride binding was present throughout the midline/intralaminar nuclei (Figures 1 and 2). The highest density of $D_{2/3}$-binding sites in the PVT was in the anterior half of the structure. More ventral midline nuclei also exhibited a moderately high density of [$^{125}$I]epidepride-binding sites (Table 1). Radioligand binding was also relatively high in a continuous lateral sweep

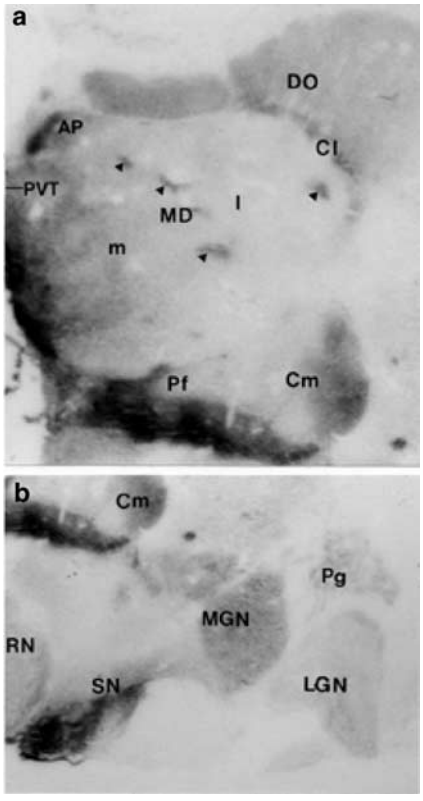


**Figure 2** [$^{125}$I]Epidepride binding in the thalamus. (a) [$^{125}$I]epidepride binding in mediodorsal nucleus is more dense in the medial half of the structure (MDm) with the lower density of $D_{2/3}$ sites laterally. Dense discontinuous radioligand binding in isolated 'islands' of the MD are present (arrowheads). Binding in the centromedian/parafascicular complex is heaviest where the centromedian is laterally positioned, while the medial portion of the nucleus shows less [$^{125}$I]epidepride binding. (b) Moderate [$^{125}$I]epidepride binding in the medial with lower binding in the lateral geniculate nuclei; labeling can also been seen in the perigeniculate nucleus (Pg). In contrast, dense binding is seen in the substantia nigra (SN).

**Table 1** The Density of [$^{125}$I]Epidepride $D_{2/3}$-Binding Sites in the Thalamus

| Region | [$^{125}$I]Epidepride binding[a] |
|---|---|
| Anterior nuc. | 0.76 ± 0.28 |
| Central lateral nuc. | 0.63 ± 0.16 |
| Centromedian nuc | 0.59 ± 0.15 |
| Lateral dorsal nuc. | 0.28 ± 0.09 |
| Lateral geniculate nuc. | 0.18 ± 0.07 |
| Medial geniculate nuc. | 0.45 ± 0.20 |
| *Mediodorsal nuc.* | |
| Medial | 0.56 ± 0.18 |
| Lateral | 0.33 ± 0.11 |
| 'Islands' | 0.70 ± 0.17 |
| Paracentral nuc. | 0.90 ± 0.18 |
| Parafascicular nuc. | 0.98 ± 0.28 |
| Parataenial nuc. | 1.46 ± 0.10 |
| *Paraventricular thalamic nuc.* | |
| Anterior | 1.48 ± 0.29 |
| Posterior | 0.86 ± 0.28 |
| Pulvinar | 0.22 ± 0.10 |
| Reticular nuc. | 0.32 ± 0.15 |
| Ventral anterior nuc. | 0.33 ± 0.11 |
| Ventral posterior | 0.27 ± 0.10 |
| *Substantia nigra* | |
| Dorsal | 1.43 ± 0.39 |
| Ventral | 0.59 ± 0.19 |
| Inferior temporal cortex | 0.50 ± 0.05 |

[a]Mean ± SD pmol/g.

from the ventral aspects of the midline thalamus to the parafascicular and central median nucleus (Figure 1 and Table 1). This band of $D_{2/3}$-binding sites extended dorsolaterally at lower density in the paracentral and central lateral nuclei, thus encircling the mediodorsal thalamic nucleus (MD).

$D_2$-like binding was lower in the MD than in the medially contiguous midline nuclei, with a clear mediolateral gradient in [$^{125}$I]epidepride binding (Figure 1 and Table 1). In addition, small 'islands' of dense [$^{125}$I]binding were seen in both the lateral and medial MD (Figure 3). The degree to which these 'islands' of high receptor binding correspond to regions that are identified by cytoarchitectonic or histochemical criteria (Ilinksy *et al*, 1985) is not clear.

The remaining thalamic nuclei exhibited low-to-moderate [$^{125}$I]epidepride binding (see Table 1 and Figures 1 and 2). The lateral tier complex, including the lateral posterior nuclei and pulvinar, showed moderate D2-type receptor binding. A moderate density of binding sites was observed in the magnocellular medial geniculate nucleus (Figure 3), in contrast to the lateral geniculate nucleus where lower

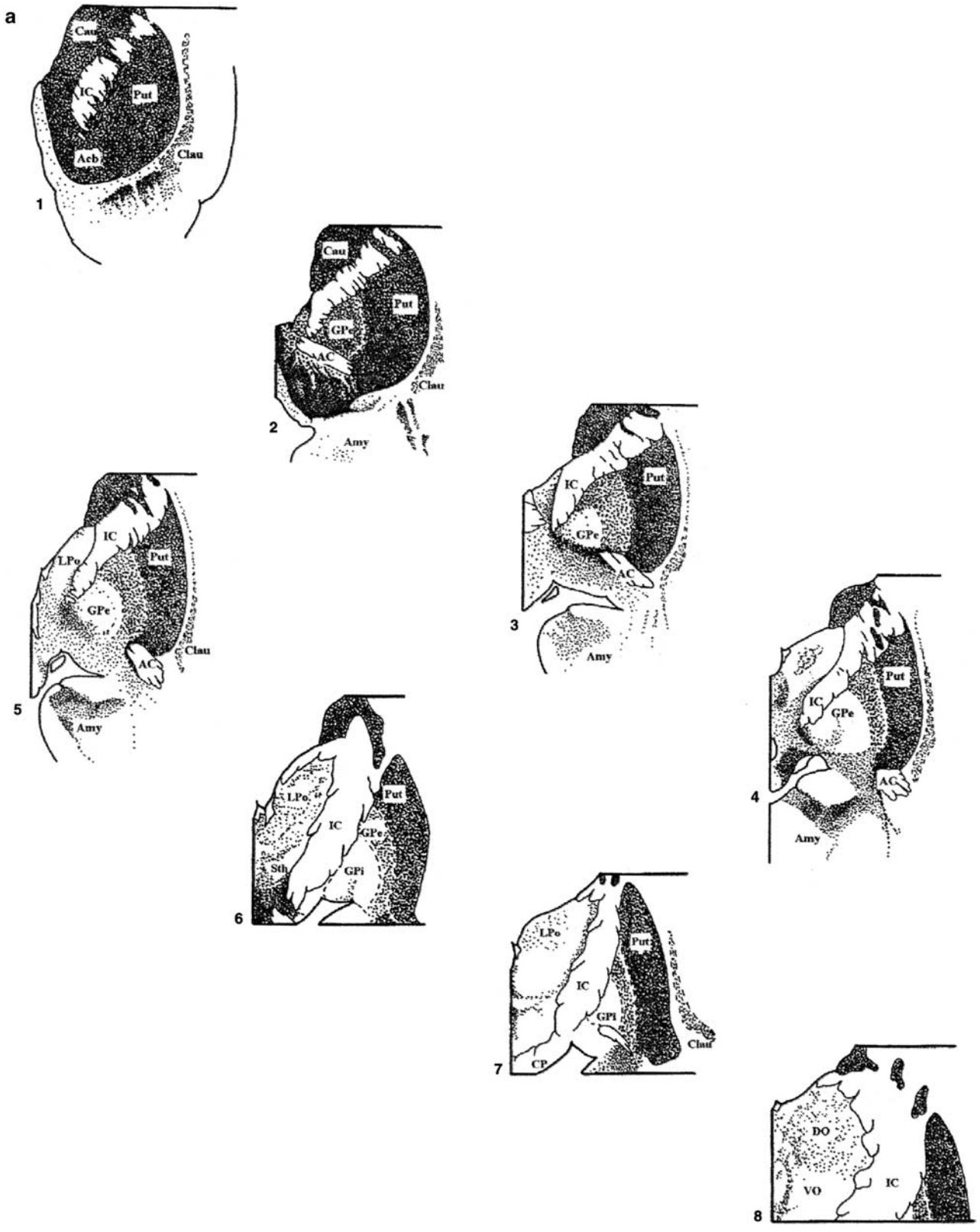


**Figure 3** Camera lucida line drawings (a–b) of [$^{125}$I]epidepride labeling of $D_{2/3}$-binding sites in coronal sections through the human thalamus. The density of [$^{125}$I]epidepride binding is depicted by different stippling densities. AC, anterior commissure; AP, principle anterior nucleus; Cau, caudate nucleus; Ce, central medial nucleus; Cl, central lateral nucleus; Cla, claustrum; Cm, centromedian; DO, dorso-oral thalamic nucleus; Dsf, dorsalis superficialis; GPe, globus pallidus, external segment; GPi, globus pallidus, internal segment; IC, internal capsule; LGN, lateral geniculate nucleus; LPo, lateroposterior nucleus; MGN, medial geniculate nucleus; mmt, mammillothalamic tract; Pf, parafascicular nucleus; Pul, pulvinar; Put, putamen; RN, red nucleus; SC, superior colliculus; SN, substantia nigra; VCe, ventro-caudal nucleus, external; VCi, ventro-caudal nucleus, internal; VIM, ventro-intermediate nucleus; VO, ventro-oral nucleus.

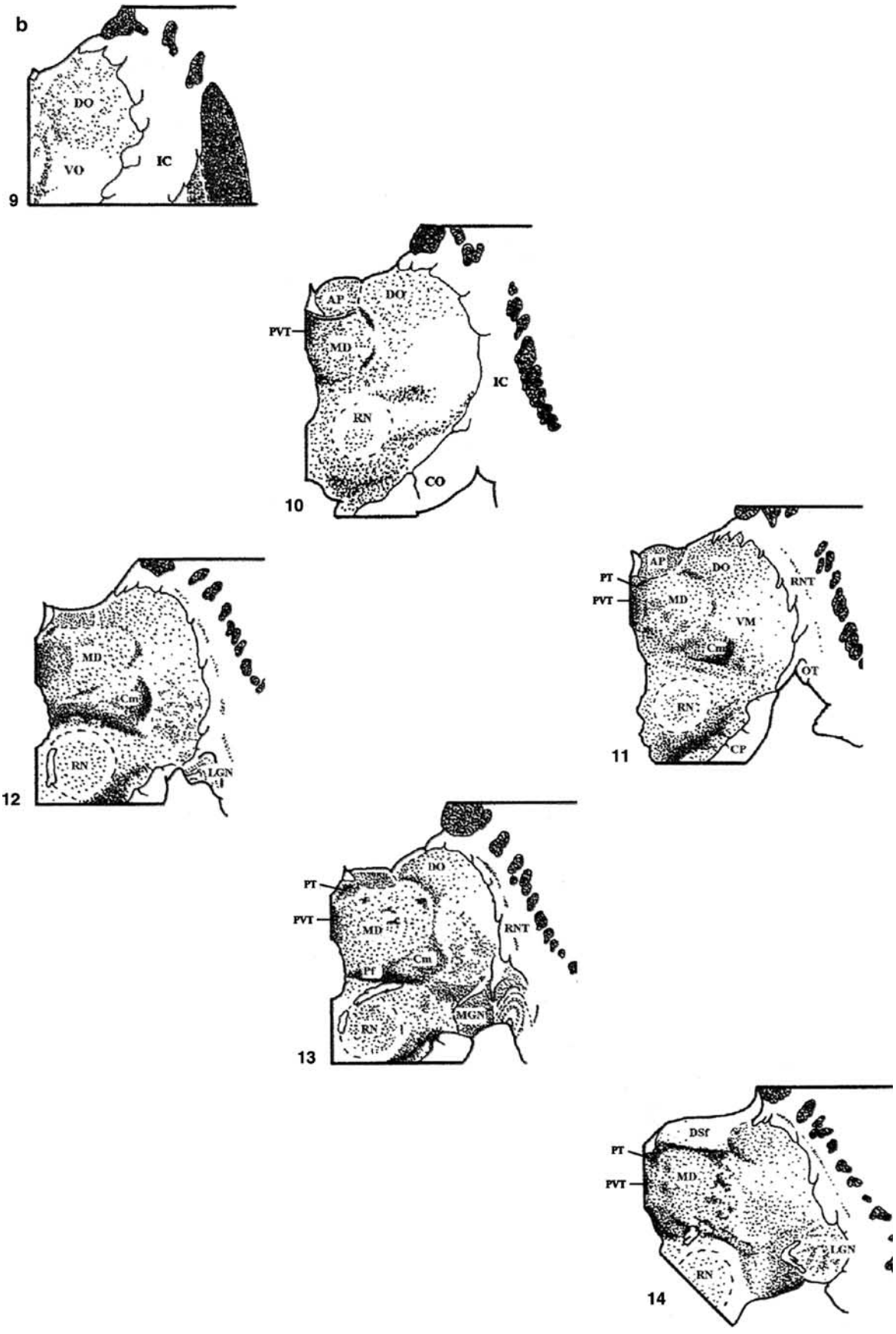


**Figure 3** Continued.

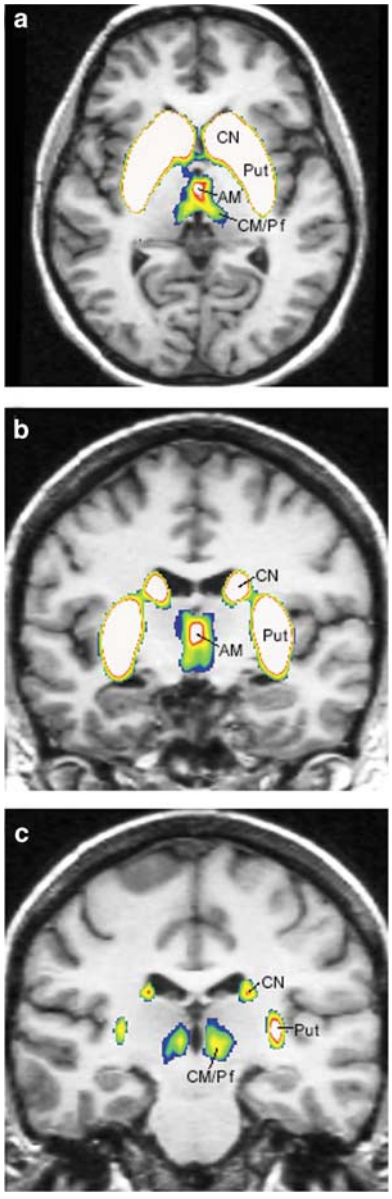


**Figure 4** Images of PET [$^{18}$F]fallypride binding potentials are shown superimposed on axial and coronal T1 weighted thin section gradient echo MRI images. The images are windowed to demonstrate binding in thalamus and basal ganglia. (a) Axial image of [$^{18}$F]fallypride binding potentials at a level approximately 2 mm above the anterior–posterior commissure line. Midline binding is seen anteriorly in the thalamus with uptake diverging laterally more posteriorly, corresponding to the region of the anterior PVT nuclei anteriorly and the centromedian/parafasicular nuclei more posteriorly. (b) Coronal images of [$^{18}$F]fallypride binding through the anterior thalamus. (c) Coronal image of [$^{18}$F]fallypride binding through the region of the centromedian/parafasicular nuclei.

densities of DA receptors were noted. A faint band of [$^{125}$I]epidepride binding was seen in the reticular nucleus; these binding sites were most apparent in the ventral aspects of the reticular nucleus. Moderate binding was also present in the parageniculate nucleus.

### *In Vivo* Studies

[$^{18}$F]Fallypride studies revealed a heterogenous pattern of radioligand accumulation in the thalamus (see Figure 4).

**Table 2** *In vivo* Binding Potentials for [$^{18}$F]Fallypride Binding to Dopamine $D_{2/3}$ Receptors in Normal Control Subjects

| Region | *In vivo* binding potential[a] |
|---|---|
| Putamen | 37.9 ± 1.46 |
| Anteromedial thalamus[b] | 4.92 ± 0.58 |
| Inferior temporal cortex | 1.62 ± 0.29 |
| Substantia nigra | 2.49 ± 0.20 |

[a]Data shown as mean ± SD.
[b]Average of anteromedial intralaminar, anterior, and medial dorsomedial nuclei.

Radioligand binding was highest in the midline thalamus, with greater densities seen in the anterior midline regions (Figure 4), in a region centered just above the anterior commissure–posterior commissure (AC–PC) line and 8 mm posterior to the anterior commissure. MRI coregistration revealed that this region corresponds to the medial wall of the thalamus, including the PVT and PT nuclei. Significantly less radioligand accumulation was present in the MD. More caudally uptake was most prominent in the area including the centromedian/parafascicular (CM/PF) nuclei, that is, approximately 25 mm posterior to the anterior commissure, 5 mm lateral to the midline, and just above the AC–PC line. Comparison of medial thalamic binding potentials to those in putamen and temporal cortex (Table 2) revealed that the *in vivo* binding potentials have a similar proportional relationship to the density of sites measured in post-mortem brain (Figure 4).

## DISCUSSION

DA $D_{2/3}$ receptors are expressed in the human thalamus in a regionally specific manner. There was a good correlation between the densities of $D_2$-like receptors as revealed by *in vitro* (autoradiographic) and *in vivo* (PET) measures. $D_2$-like-binding sites were present in relatively high densities in so-called 'nonspecific' thalamic nuclei, but were present in relatively low density in motor nuclei. The highest densities of $D_2$-like receptors were present in thalamic nuclei that project to the striatal complex and mesocorticolimbic DA terminal fields, suggesting that thalamic $D_2$-like receptors are in a position to modulate limbic and basal ganglia function. This observation is consistent with a variety of data pointing to the involvement of thalamic DA systems in neuropsychiatric disorders.

### Technical Issues

Epidepride ligands have been used extensive for both *in vitro* and *in vivo* studies assessing the distribution and levels of $D_2$-like DA receptors. [$^{125}$I]Epidepride has a high affinity for $D_2$ and $D_3$ receptors but not $D_1$, $D_2$, or $D_4$, $\alpha_1$ noradrenergic, 5-$HT_{2a/c}$ serotonergic, or $GABA_A$ sites (Kessler *et al*, 1993a, b); approximately 10% of [$^{125}$I]epidepride binding in certain cortical regions appears to reflect interaction with $\alpha_2$ noradrenergic receptors (Joyce *et al*, 1991). We did not distinguish between $D_2$ and $D_3$ receptors in our autoradiographic studies because we wanted these

data to reflect as closely as possible thalamic $D_{2/3}$-binding sites as seen in the PET studies.

The subjects used in our study were free of neurological or psychiatric disorders. They were also relatively young, thus minimizing any age-related declines in thalamic DA receptor densities (Inoue *et al*, 2001).

## Comparison with Previous Studies

Our autoradiographic studies confirm and extend previous descriptions of the presence and distribution of $D_2$-like receptor binding in the human thalamus. Hall *et al* (1996a, 1997) used autoradiographic methods to describe the distribution of brain [$^{125}$I]epidepride-binding sites. They noted that the greatest density of extrastriatal $D_2$-like receptors was found in the thalamus, particularly in what they termed the PT. Our data agree well with this conclusion and indicate that the PVT and PT have the highest density of $D_2$-like receptors in the thalamus. Our data extend the observations of Hall and colleagues by detailing the distribution of $D_2$-like sites throughout the thalamus, both across and within individual thalamic nuclei. For example, we described the hitherto unappreciated pattern of binding in the mediodorsal nucleus, where we observed a moderate level of $D_2$-like-binding sites in a distinct mediolateral gradient, upon which were superimposed 'islands' of high-density $D_{2/3}$ binding.

Our [$^{18}$F]fallypride PET data confirm the presence of $D_2$-like-binding sites in the human brain. Previous SPECT (Kornbuher *et al*, 1995; Kuikka *et al*, 1997) and PET (Christian *et al*, 2000; Farde *et al*, 1997; Halldin *et al*, 1995; Mukherjee *et al*, 2001; Yousef *et al*, 1995) studies using various ligands have reported low-to-moderate densities of $D_2$-like-binding sites in the thalamus. Consistent with the dopaminergic nature of these binding sites, Yousef *et al* (1995) reported that the $D_2$-like antagonist haloperidol blocked thalamic radioligand accumulation.

Our PET imaging studies extend previous *in vivo* imaging studies of the thalamus by revealing a heterogeneous distribution of $D_{2/3}$ receptors in the human thalamus with relatively high resolution. We found an anteroposterior gradient in [$^{18}$F]fallypride accumulation, with the highest accumulation being seen in the rostral half of the dorsal midline thalamic nuclei, a region corresponding to the PVT and PT; in our autoradiographic data we found a significantly greater density of binding sites in the anterior half of the PVT. More caudally in the thalamus we observed relatively high accumulation of the radioligand in a lateral extension from the midline (in the vicinity of the reuniens nucleus) to the CM/PF complex.

## Dopaminergic Receptors and the Dopaminergic Innervation of the Human Thalamus

Neither [$^{125}$I]epidepride nor [$^{18}$F]fallypride distinguish between $D_2$ and $D_3$ receptors. Both receptors appear to be present in the human thalamus, although the relative proportions of the two is unclear. Hall *et al* (1996b) failed to find any specific $D_3$ receptor binding in the human thalamus, while Herroelen *et al* (1994) reported the presence of specific $D_3$ but not $D_2$-binding sites in the human thalamus. Gurevich and Joyce (1999) reported that both $D_3$ receptors predominate in several thalamic areas, but in some areas (central lateral and central medial nuclei) only $D_2$ sites are present; they did not examine the PVT and PT because blocking of the brain cut through the midline thalamus. D2-like mRNAs have been reported in the human thalamus, with some neurons of the midline, anteroventral, and mediodorsal nuclei expressing both $D_3$ and $D_2$ mRNAs (Gurevich and Joyce, 1999). It seems likely that the relatively minor discrepancies concerning $D_{2/3}$ receptor distributions in the human thalamus reflect the use of different ligands (Flietstra and Levant, 1998; Hall *et al*, 1996b, 1997). Although additional studies are needed to clarify the relative contribution of $D_2$ and $D_3$ receptors to the total pool of thalamic $D_2$-like-binding sites, most studies suggest that $D_3$ receptors are relatively enriched in the midline and anteroventral nuclei, whereas $D_2$ receptors may be more abundant in other thalamic nuclei.

We have focused our studies on $D_2$-like receptors in the thalamus, and did not examine $D_1$-like receptors, including $D_1$ and $D_5$ receptors. Previous studies have indicated that there is diffuse low abundance thalamic expression of $D_1$ receptor mRNA in primate species, including humans (Choi *et al*, 1995; Meador-Woodruff *et al*, 1999). However, some thalamic nuclei in humans, including several in which we observed relatively high $D_2$-like receptor gene expression (dorsomedial, anterior, central medial), express $D_1$ mRNA at somewhat higher levels than others (reticular and ventral nuclei) (J Meador-Woodruff, personal communication). Expression of the $D_5$ transcript is very low in the thalamus.

The presence of DA-like receptors in the human thalamus implies the presence of a thalamic DA innervation. In the rat there is a discrete DA innervation of the midline thalamic nuclei, particularly the PVT; the density of DA-immunoreactive fibers decreases sharply in more ventral midline nuclei and at the PVT–MD border (Groenewegen, 1988). DA axons in the rat PVT arise predominantly from hypothalamic sources, although a few ventral tegmental area DA neurons also project to the PVT (Otake and Nakamura, 1998; Takada *et al*, 1990). In the human thalamus early data on thalamic DA was ambiguous. Oke *et al* (1992) reported very low tissue concentrations of DA in the human thalamus, comparable to that present as a precursor pool in the noradrenergic and adrenergic thalamic innervations (Bosler *et al*, 1987; Rico and Cavada, 1998). However, post-mortem studies sharply underestimate DA concentrations relative to concentrations of the amine in biopsy samples obtained during surgical interventions (Goldstein *et al*, 1988). An *in vivo* microdialysis study of the human thalamus in PD patients reported that extracellular DA levels could be reliably detected in the thalamus (Meyerson *et al*, 1990). Recent anatomical studies found a significant density of dopamine transporter (DAT)-like immunoreactive axons in the thalamus, particularly the midline/intralaminar nuclei and the MD (Freeman *et al*, 2001; Melchitzky and Lewis, 2001). These observations are consistent with PET data suggesting the presence of DAT-binding sites in the human thalamus (Gunther *et al*, 1997), and the finding that methylphenidate administration reduces [$^{11}$C]raclopride binding in the thalamus (Volkow *et al*, 1997), consistent with displacement of the radioligand by released DA.

There are some mismatches between the distribution of $D_{2/3}$ receptors as revealed by our autoradiographic studies and the distribution of the human thalamic DA innervation as revealed by DAT immunohistochemistry. We found that the density of $D_{2/3}$ receptors in the MD followed a mediolateral gradient, but DAT-immunoreactive axons are localized most densely to the lateral and ventral MD (Freeman *et al*, 2001; Melchitzky and Lewis, 2001), and are in low density in the medial MD and virtually absent from the midline nuclei. Similarly, we found that the $D_{2/3}$ receptors in the reticular nucleus were present in very low density but most apparent in the ventral reticular nucleus, whereas DAT-immunoreactive axons are distributed more heavily to the middle third of the nucleus. It appears most likely that these discrepancies are due to the use of DAT as a marker of DA neurons. DAT mRNA levels are low or below detection thresholds in cells of the medial VTA (Little *et al*, 1998), and similarly some midbrain DA neurons (especially in the medial VTA) are not DAT immunoreactive (Ciliax *et al*, 1999).

## Functional Implications

The adjective 'nonspecific' is a misnomer when applied to the midline/intralaminar nuclei (Groenewegen and Berendse, 1994). The efferent projections of different midline and intralaminar thalamic nuclei are to regionally distinct regions in the forebrain (Berendse and Groenewegen, 1990, 1991; Krout *et al*, 2002; Moga *et al*, 1995; Su and Bentivoglio, 1990), and relatively few of the neurons in these nuclei collateralizing to innervate multiple targets (Bubser and Deutch, 1998; Calderazzo *et al*, 1996). Among the projection targets of the midline/intralaminar nuclei are distinct territories in the striatal complex, prefrontal cortex, amygdala, and hippocampus (Berendse and Groenewegen, 1990; Bubser and Deutch, 1998; Calderazzo *et al*, 1996; Jayaraman, 1985). These areas also all receive DA inputs from the midbrain (Deutch *et al*, 1988, Moore and Bloom, 1978; Swanson, 1982). The thalamic neurons that project to forebrain DA terminal field regions are glutamatergic (Christie *et al*, 1987; Fuller *et al*, 1987) and can readily influence dopaminergic function (Calabresi *et al*, 1997; Whitton, 1997).

The origins of DA inputs to thalamic nuclei in the human are not known. The widespread distribution of thalamic $D_2$-like receptors suggests that there may be a comparably broad distribution of DA afferents to the human thalamus. The PVT and other midline/intralaminar nuclei have long been known to receive information from brainstem reticular formation neurons (Jasper, 1949; Krout *et al*, 2002; Niimi *et al*, 1990). Single cholinergic reticular formation neurons collateralize to innervate both the PVT and ventral tegmental area (Bolton *et al*, 1993), thus providing a means by which reticular core information can directly (through the ventral tegmental area) and indirectly (via PVT projections to forebrain DA terminal fields) regulate forebrain dopaminergic function. These anatomical data suggest that signaling through DA receptors on midline thalamic neurons may convey information to mesocorticolimbic DA terminal fields, particularly the frontal cortices, and thus potentially be involved in the attention deficits seen in schizophrenia (Kornetsky and Orzack, 1978; Matthysse, 1978). Consistent with this speculation is the fact that neurons of the PVT and other midline/intralaminar nuclei are targets of atypical antipsychotic drugs (Cohen *et al*, 1998; Deutch *et al*, 1995). In addition, several recent studies have reported decreased numbers of neurons in the mediodorsal nucleus (Pakkenberg, 1990; Popken *et al*, 2000, Young *et al*, 2000).

A number of findings suggest that DA $D_3$ receptors in midline thalamic nuclei may play an important role in the actions of psychostimulants (see Deutch *et al*, 1998). Among the afferents to the midline nuclei are those arising from the hypothalamus and nucleus tractus solitarius (Krout *et al*, 2002; Ruggiero *et al*, 1998), which relay interoceptive information to the PVT and thus allow the PVT to integrate exteroceptive (via the reticular formation) and interoceptive cues. The ability to coordinate afferent activity conveying both exteroceptive and interoceptive information may be of critical importance in drug abuse, and lesions of the PVT block the conditioned locomotor response associated with cocaine administration (Young and Deutch, 1998). Although neurons in many brain areas are activated in response to acute cocaine challenge, the PVT is among the few sites that is activated in animals exposed to a neutral stimulus that was previously paired with cocaine (Brown *et al*, 1992). These data and corresponding *in vivo* imaging data (Volkow *et al* 1997; Wang *et al*, 1997) argue for medial thalamic involvement in the drug craving cued by environmental stimuli.

There has been considerable interest in thalamic involvement in PD because the basal ganglia gain access to the cortex via the thalamus. Recent data indicate that thalamic involvement may be more widespread in PD than previously suspected. Thus, in addition to imaging data indicating changes in ventrolateral thalamic regional cerebral blood in response to L-DOPA that are associated with movement (Feigin *et al*, 2002; Hershey *et al*, 1998; Pakkenberg, 1990; Popken *et al*, 2000; Young *et al*, 2000), changes in midline/intralaminar nuclei have also been found. Henderson *et al* (2000) reported a striking decrease in the numbers of neurons in the CM/PF complex in PD patients. Moreover, recent data suggest the involvement of specific thalamic dopaminergic systems. The density of DAT-immunoreactive axons is decreased in the thalamic reticular nucleus of PD patients (Freeman *et al*, 2001), and *in vivo* imaging data indicate a decrease in $D_2$-like receptor density in the medial thalamus of patients with advanced but not early PD (Kaasinen *et al*, 2000).

One final function in which thalamic DA receptors may play a role is pain perception. The thalamus is a key nociceptive relay, and electrophysiological studies have revealed that neurons in the CM/PF complex respond to nociceptive stimuli (Dong *et al*, 1978; Willis, 1985). The presence of D2-like receptors in the CM/PF complex offers a mechanism for the reported involvement of dopaminergic systems in the subjective components of pain (Chudler and Dong, 1995; Kamei and Saitoh, 1996). However, a recent imaging study of striatal and extrastriatal DA receptors reported that the $D_2$ binding potential in the putamen but not thalamus is associated with pain responses (Hagelberg *et al*, 2002). It is possible that intralaminar thalamic neurons respond to DA and convey this information to the striatum (Matsumoto *et al*, 2001).

## Summary

DA $D_2$-like receptors were present in moderately high density in several nuclei of the human thalamus. The pattern of expression of $D_2$-like receptors was heterogeneous, being most enriched in the midline and intralaminar nuclei that give rise to limbic forebrain regions. The presence of these $D_2$-like receptors suggests that dopaminergic mechanisms may play an important role in neuropsychiatric disorders that involve a dysfunction of thalamocortical and thalamostriatal systems.

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