Dopamine D₁ Agonist Activates Temporal Lobe Structures in Primates

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Black, Kevin J., Tamara Hershey, Mokhtar H. Gado, and Joel S. Perlmutter. Dopamine D₁ agonist activates temporal lobe structures in primates. J Neurophysiol 84: 549–557, 2000. Changes in the function of dopamine D₁-influenced neuronal pathways may be important to the pathophysiology of several human diseases. We recently developed methods for averaging functional imaging data across nonhuman primate subjects; in this study, we apply this method for the first time to map brain responses to experimental dopamine agonists in vivo. Here we report the use of positron emission tomography (PET) in seven normal baboons to measure the regional cerebral blood flow (rCBF) responses produced by an acute dose of the dopamine D₁ full agonist SKF82958. The most significant rCBF increases were in bilateral temporal lobe, including amygdala and superior temporal sulcus (6–17%, P < 0.001). Blood flow decreased in thalamus, pallidum, and pons (4–7%, P = 0.001). Furthermore the rCBF responses were dose-dependent and had a half-life of ~30 min, similar to that reported for the drug’s antiparkinsonian effects. Absolute whole-brain blood flow did not change, suggesting that these local changes in rCBF reflect neuronal rather than direct vascular effects of the agonist. The prominent temporal lobe response to a D₁ agonist supports and extends our recent observations that levodopa produces prominent amygdala activation both in humans and in other primates. We speculate that levodopa may exert its known effects on mood in humans through increased amygdala activity, mediated in part by D₁ receptors.

INTRODUCTION

Dopamine D₁-like receptors (D₁ and D₂) may be important in several human diseases, including movement disorders (Young and Penney 1993), drug abuse (Self et al. 1996), major depression (Gambarana et al. 1995), and schizophrenia (Okubo et al. 1997). In addition, D₁ receptors regulate working memory function in primates (Williams and Goldman-Rakic 1995) and are thought to be important in the control of normal movement and appetitive behavior (Jackson and Westland-Danielsson 1994). D₁ receptors are distributed anatomically so as to permit this wide functional range. They are most densely located in striatum (preferentially on striatonigral projection neurons) and substantia nigra but at lower levels are widely distributed in cortex, where they substantially outnumber D₂ receptors (Bergson et al. 1995; Gerfen et al. 1995; Levey et al. 1993; Surmeier et al. 1996; Waszczak et al. 1998). Dopaminergic cortical afferents appear to terminate on dendrites of pyramidal neurons so as to potentially alter projection neuron responses to excitatory inputs (Goldman-Rakic et al. 1989, 1990, 1992).

Abnormal function of D₁-influenced neuronal pathways could arise from alterations in D₁ receptors. However, other changes, such as in co-modulators or second messengers, can produce functionally important changes in these pathways without altering receptor binding (Goulet et al. 1996; LaHoste and Marshall 1992; Morelli et al. 1990). Ideally one would like to probe the overall function of D₁-influenced neuronal pathways in vivo. One approach is to administer a receptor-specific agonist and evaluate its acute effects on regional cerebral blood flow (rCBF) or metabolism as an index of a regional change in neural activity.

The utility of this approach has been demonstrated by studies examining regional metabolic responses to an acute dose of various dopaminergic drugs (Ingvar et al. 1983; Kelly and McCulloch 1987; McCulloch 1982, 1984; Pizzolato et al. 1987; Sharkey et al. 1991; Trugman and Wooten 1986; Trugman et al. 1991), including the partial D₁ agonist SKF38393 (Engber et al. 1993; Morelli et al. 1993; Palacios and Wiederhold 1985; Trugman and James 1992, 1993; Trugman and Wooten 1987; Trugman et al. 1989). Most of these studies used the ex vivo [14C]-2-deoxyglucose (2DG) autoradiographic technique in normal or 6-hydroxydopamine (6OHDA)-lesioned rats. These studies have revealed substantial information about the rodent brain’s functional response to dopaminergic lesions or treatment (Orzi et al. 1993; Trugman 1995; Wooten and Trugman 1989). Notably, this method is sensitive to functional changes that cannot be detected by measuring receptor binding alone (McCulloch 1982, 1984; McCulloch and Teasdale 1979; Trugman and James 1992).

We have extended these studies to the living primate brain by assessing the acute effects of various dopaminomimetics on rCBF using H₂¹⁵O and positron emission tomography (PET) in humans and nonhuman primates (Black et al. 1996b, 1997a; Hershey et al. 1997, 1998; Perlmutter 1995; Perlmutter et al. 1993). Regional blood flow is a useful marker as it can be measured frequently and quantitatively, and alterations in rCBF have been shown to reflect regional metabolic changes in the presence of dopaminergic drugs (Azuma et al. 1988; McCulloch and Harper 1977; McCulloch et al. 1982). Many other investigators have also studied drug effects with PET,

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though not with D₁ agonists (see selected references in Black et al. 1997a; Perlmutter 1997).

We recently developed and validated methods for averaging functional imaging studies in nonhuman primates into a common atlas space (Black et al. 1996a, 1997b). Such methods enhance signal-to-noise properties for identification of brain responses in either physiological or pharmacological activation studies (Fox et al. 1988; Raichle et al. 1991). Image averaging across subjects also allows one to deal with anatomic and functional variability and to map physiologic neuronal responses without a priori knowledge of the sites of action in the brain. Similar methods have long been available for humans (Fox et al. 1985) and were widely adopted due to these advantages. Their availability in other species now permits us to perform experiments such as mapping brain responses to an experimental drug not available for human use.

In this report, we describe the effects of the dopamine D₁ full agonist SKF82958 (Andersen and Jansen 1990; Bergman et al. 1996) on rCBF in normal nonhuman primates. The goal of the study was to define which brain regions are most influenced by D₁ agonists in the normal primate brain. To our knowledge, this is the first autoradiographic study in primates of D₁ agonist effects, and the first study to analyze functional imaging data in a group of different nonhuman subjects using stereotaxy and recent statistical developments.

**METH O D S**

**PET image acquisition**

All PET studies were performed on a Siemens 953B scanner in two-dimensional (2D) wobble mode. This scanner records data simultaneously for 31 slices with a center-to-center slice separation of 3.4 mm (Mazoyer et al. 1991; Spinks et al. 1993). For each study, we acquired a transmission scan for individual attenuation correction with rotating rod sources of activity containing ^68 Ge/^68 Ga. PET images were reconstructed to an initial transverse full width half-maximum (FWHM) resolution of 5.4 mm using a ramp filter (final image resolution was 8 mm; see following text). CBF was measured using arterial sampling and a 40-s emission scan following the intravenous bolus injection of ~10 ml of saline containing 30–50 mCi of ^15 O-labeled water, a method previously validated in baboons (Herscovitch et al. 1983; Raichle et al. 1983; Videen et al. 1987).

**Scan protocol**

With the prior approval of the Washington University Animal Studies Committee, we performed eight PET studies in five normal baboons sedated with 70% inhaled N₂O. Each study included multiple measurements of rCBF; a total of 89 measurements was included in these studies. No physiologic PET scans were obtained until the first study was performed. No physiologic PET scans were obtained until the first study was performed; a total of 89 measurements was included in the statistical analysis if the voxel intensity in each image was >80% of the mean intensity in that image. This resulted in a search volume of 187 ml, which is appropriate given a baboon atlas brain volume of ~165 ml (unpublished data). As images were already intensity normalized, no further global normalization was performed in SPM96. Absolute global (whole-brain) blood flow was quantified in a subset of scans using published methods (Black et al. 1997a; Herscovitch et al. 1983; Raichle et al. 1983; Videen et al. 1987).

**Statistical methods**

For regional analysis of the PET data, we used normalized PET counts, which are linearly related to blood flow (Fox and Mintun 1989). This is the most common approach to analysis of PET[^15 O]water studies. We took the additional step of quantifying absolute brain blood flow to confirm that this method is appropriate (see RESULTS and DISCUSSION). If absolute global flow does not change, the absolute and normalized regional values are redundant. In addition, the absolute rCBF values are noisier since they include several additional measurement steps.

Normalized PET images were transformed to a common atlas space and resampled to 1-mm cubic voxels (Black et al. 1996a, 1997b; Davis and Huffman 1968). After this step (which also adds spatial filtering via registration error and interpolation), a three-dimensional (3D) Gaussian filter with 6.0 mm FWHM kernel was applied using a freely available software package (SPM96 with random effects kit) (Friston et al. 1996; Holmes and Friston 1998). The final image resolution was estimated by SPM96 as ~8 mm. The primary comparison was between baseline scans and scans after 100 μg/kg SKF82958. Voxels in atlas space were included in the statistical analysis if the voxel intensity in each image was ≥80% of the mean intensity in that image. This resulted in a search volume of 187 ml, which is appropriate given a baboon atlas brain volume of ~165 ml (unpublished data). As images were already intensity normalized, no further global normalization was performed in SPM96. At each included voxel, SPM96 computed a random effects statistic corresponding roughly to a paired t-test and transformed this statistic to a Z score. An initial magnitude threshold of Z ≥ 2 was applied, and SPM96 computed the probability that each region of contiguous voxels attaining this magnitude would have occurred by chance given the size in voxels of the activated region. Regional activations were considered significant with a corrected probability of P < 0.05. This strategy has been validated using simulations (Friston et al. 1994, 1996). Representative peaks within each region, separated by ≥8 mm, were reported by SPM96, and the most significant peaks (i.e., those for which P < 0.05 after voxelwise correction for multiple comparisons based on Z-score magnitude only) are given in Table 1. Points lying outside the brain were ignored. Amplitude and time-course data for selected peaks were computed based on an 8-mm-diam spherical VOI centered on the peak coordinate reported by SPM96.

**Calculation of half-life of PET responses**

For the most prominent activations, a half-life of the PET response was computed as follows. The rCBF response in each scan, expressed as a percentage change from the average baseline rCBF from that study, was plotted against the elapsed time from the administration of 100 μg/kg SKF82958 to the beginning of the scan (Fig. 2A). A two-parameter exponential decay model, ΔrCBF = A × 2⁻ᵗ/τ₀, was
TABLE 1. Regions significantly activated by 100 μg/kg SKF82958

<table>
<thead>
<tr>
<th>Region (Peaks)</th>
<th>Corrected ( P )</th>
<th>( k (Z) )</th>
<th>Peak Location ((x\ y\ z))</th>
<th>Change in rCBF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral temporal lobes</td>
<td>0.000</td>
<td>28360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. superior temporal sulcus*</td>
<td>0.000</td>
<td>7.11</td>
<td>33.5</td>
<td>10.5</td>
</tr>
<tr>
<td>L. superior temporal gyrus*</td>
<td>0.000</td>
<td>6.80</td>
<td>-25.5</td>
<td>20.5</td>
</tr>
<tr>
<td>R. superior temporal gyrus</td>
<td>0.000</td>
<td>6.71</td>
<td>21.5</td>
<td>21.5</td>
</tr>
<tr>
<td>L. lateral amygdala</td>
<td>0.000</td>
<td>6.65</td>
<td>-15.5</td>
<td>24.5</td>
</tr>
<tr>
<td>R. middle temporal gyrus*</td>
<td>0.000</td>
<td>6.42</td>
<td>34.5</td>
<td>1.5</td>
</tr>
<tr>
<td>R. superior temporal sulcus*</td>
<td>0.000</td>
<td>6.40</td>
<td>29.5</td>
<td>-1.5</td>
</tr>
<tr>
<td>R. superior temporal gyrus*</td>
<td>0.000</td>
<td>6.03</td>
<td>32.5</td>
<td>18.5</td>
</tr>
<tr>
<td>L. superior temporal gyrus</td>
<td>0.000</td>
<td>5.76</td>
<td>-25.5</td>
<td>12.5</td>
</tr>
<tr>
<td>L. superior temporal gyrus*</td>
<td>0.027</td>
<td>4.57</td>
<td>-26.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Brainstem/basal ganglia</td>
<td>0.001</td>
<td>12108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. globus pallidus</td>
<td>0.018</td>
<td>4.67</td>
<td>12.5</td>
<td>16.5</td>
</tr>
<tr>
<td>L. globus pallidus</td>
<td>0.021</td>
<td>4.63</td>
<td>0.5</td>
<td>12.5</td>
</tr>
<tr>
<td>R. inferior central thalamus/GPM</td>
<td>0.040</td>
<td>4.47</td>
<td>-6.5</td>
<td>12.5</td>
</tr>
<tr>
<td>L. thalamus (ventrolateral n.)</td>
<td>0.045</td>
<td>4.44</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>R. parietal lobe*</td>
<td>0.045</td>
<td>4.44</td>
<td>16.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Values in second and third columns for bilateral temporal lobes and brainstem/basal ganglia are corrected \( P(k, Z) \) and \( k \), respectively. Corrected \( P(k, Z) \) is the multiple-comparisons-corrected \( P \) value for this region of \( k \) contiguous voxels surpassing \( Z = 2 \). Corrected \( P(Z) \) is a post hoc statistic representing the corrected \( P \) value, based on magnitude and image smoothness, for the \( Z \) value at the given voxel. The \( x, y, \) and \( z \) coordinates are extrapolated from the Davis and Huffman atlas (1968), as described elsewhere (Black et al. 1997b, 1999b). The entry “0.000” indicates a corrected \( P \) value <0.0005. L, left; R, right. Peaks marked by an asterisk (*) indicate points not included in the Davis and Huffman (1968) atlas; the description of these points is taken from a representative magnetic resonance image in atlas space (Black et al. 1997b). GPM, periventricular midbrain gray matter; rCBF, regional cerebral blood flow.

fit to the data using SSPS for Windows 7.5.1 (SPSS, Chicago, IL), giving the half-life \( B \) and an estimate \( r \) of goodness of fit.

RESULTS

Regional activations

Two areas of significant changes in rCBF were observed following 100 μg/kg SKF82958 (see Table I and Fig. 1). The \( D_1 \) agonist activated a diffuse area of temporal cortex bilaterally (corrected \( P < 0.001 \)), extending into amygdala and hippocampus but also involving a large area of lateral temporal lobe along the superior temporal sulcus (STS). A significant decrease in rCBF was observed in the brainstem/basal ganglia (corrected \( P = 0.001 \)) with the most significant decreases centered on the globus pallidus and thalamus.

Time course of activations

By plotting relative change in rCBF against time, we observed that the rCBF changes generally followed a pharmacologically sensible time course, reaching a peak early and then falling over time (Fig. 2A). Assuming linear kinetics, one can also compute a half-life \( t_{1/2} \) for the individual rCBF responses by fitting a first-order exponential curve to the data. For some regions, this plot was noisy, with \( r < 0.5 \), and consequently estimates of \( t_{1/2} \) were unreliable. For regions in which \( r \geq 0.5 \) (such as R. and L. superior temporal gyrus and L. amygdala), the \( t_{1/2} \) of the PET response was between 26 and 35 min (Fig. 2A). This corresponds well to a 35- to 60-min duration of antiparkinsonian effect of subcutaneous SKF82958 in cynomolgus monkeys, which presumably reflects striatal action of the drug (Blanchet et al. 1994).

Dose-response curve

A dose-response curve for the most significant PET response is shown in Fig. 2B. Recall that peak locations were obtained independent of the PET responses to 1 or 10 μg/kg SKF82958.

Control experiments

Since the order of scans could not be randomized (i.e., baseline scans always preceded drug), the significant rCBF changes described above could be due either to the \( D_1 \) agonist or to unknown factors associated with the passage of time from the pre- to postdrug scans. Evidence against the latter interpretation includes the following. First, the two studies that proceeded directly from baseline scans to post-100 μg/kg SKF82958 scans followed the PET responses of right STS, +13.6%; thalamus, +4.1%, left amygdala, +7.5%. These are nearly identical to the PET responses in the remaining studies in which the post-100 μg/kg SKF82958 scans followed the baseline scans by 1.5–4 h. Second, the rCBF changes after the highest dose tended to peak early and then decline over time (see Fig. 2A), whereas the opposite would be expected if the changes were nonspecific. Finally, in three control studies in which no dopamine agonist was administered, the average change in rCBF over a similar time interval was: right STS, +5.0%, thalamus, –3.7%, and left amygdala, +1.2%; noticeably smaller than the responses observed after 100 μg/kg SKF82958.

Absolute global blood flow

There was no significant change in absolute global cerebral blood flow with 100 μg/kg SKF82958. Expressed as ml × 10^{-2} × g^{-1} × min^{-1}, global blood flow at baseline was 67.5 ± 15.7 (mean ± SD, \( n = 17 \) scans), and after 100 μg/kg SKF82958 was unchanged at 67.2 ± 19.1 (\( n = 20 \)).

DISCUSSION

The most significant change in rCBF following administration of a dopamine \( D_1 \) agonist in primates was a diffuse activation of bilateral temporal lobes, including increases in amygdala and superior temporal sulcus. The increases were dose dependent and were not due to a “priming” effect of the
preceding smaller doses or to passage of time between baseline and postdrug scans. A time-response curve could be extracted from the data, allowing us to estimate the $t_{1/2}$ of the drug’s effects on rCBF.

**Bilateral temporal lobe activation**

The largest responses were observed in both lateral and medial temporal lobe bilaterally. It may appear surprising that the D$_1$ agonist produced such a prominent activation in the amygdala, but this supports and extends observations we have made in other primate studies. Most rodent pharmacologic activation studies with dopaminergic agents have focused on changes in subcortical structures, especially in the lentiform nuclei, substantia nigra, or lateral habenula (McCulloch 1982, 1984; Orzi et al. 1993; Trugman 1995; Wooten and Trugman 1989). Although no prior reports have focused on amygdala activation by dopaminergic agents, we have recently discovered that the amygdala is a major site of increased blood flow following levodopa administration in each of four primate groups: normal humans, chronically treated patients with Parkinson’s disease (PD), an awake monkey, and sedated baboons (Hershey et al. 1997, 1998). This finding is also consistent with the data of McCulloch et al. (1982), which demonstrate a dose-dependent metabolic increase in the anterior amygdala (among numerous other regions) after administration of the

![FIG. 1. A statistical map created by SPM96 (color) is overlaid on a magnetic resonance image (MRI) in atlas space (grayscale). Subject’s right is shown on the right side of axial or coronal images. Coronal (A) and axial views (B) of the most significant regional cerebral blood flow (rCBF) increase, along the right superior temporal sulcus. Sagittal (C) and axial views (D) with crosshairs on the atlas coordinates of the center of the left amygdala (Black et al. 1999a). Sagittal (E) and axial views (F) of the region of rCBF decrease with crosshairs on the peak Z value in thalamus.](https://j Physiology.org/article-pdf/552-6.pdf)

![FIG. 2. Selected rCBF responses plotted against time after drug (A) or intravenous dose (B) of SKF82958. Plots correspond to SPM96 peak in right superior temporal gyrus (A), atlas coordinate (21.5, 21.5, −9), and SPM96 peak in right superior temporal sulcus (B), atlas coordinate (33.5, 10.5, 4). See Experimental procedures and DISCUSSION for details.](https://j Physiology.org/article-pdf/552-6.pdf)
nonselective dopamine agonist apomorphine to normal rats. Our results with SKF82958 may indicate that the effect of these nonspecific dopaminergic agents in the amygdala is mediated at least in part by D1 receptors.

This observation begs the question, which D1 receptors? The question is important because regional alterations of blood flow following administration of dopaminetics do not correspond well with the local density of dopamine receptors (McCulloch 1982, 1984). Rather, a regional metabolic change appears to derive from changes in the firing rate of axons terminating in the region (Ackermann et al. 1984; Eidelberg et al. 1997; Schwartz et al. 1979). Thus a metabolic change in a given area, after administration of a dopamine agonist, may be mediated either by distant dopamine receptors that modulate firing of afferents or by local receptors, such as presynaptic receptors or receptors on local interneurons.

Increased amygdala rCBF following SKF82958 may reflect increased local neuronal activity following stimulation of D1 receptors in the amygdala (Levey et al. 1993). Alternatively, positive feedback in amygdala-cortical-atrial neuronal pathways may be stimulated by D1 effects at any of these three sites, which might increase neuronal activity in all three areas (Price et al. 1996).

What might be the functional relevance of the prominent amygdala response to a D1 agonist? There is substantial evidence for the amygdala’s role in emotion, including the finding of abnormal amygdala rCBF at rest in patients with major depression (Drevets and Raichle 1994; Drevets et al. 1992; Price et al. 1996). In our PET studies with PD patients, the amygdala response to levodopa was more pronounced in a patient group with longstanding disease and chronic treatment (Hershey et al. 1998), although none of those subjects had evidence of depression when studied. It is tempting to speculate that an increase in the amygdala’s response to individual doses of levodopa may relate to the observation that some patients with long-standing, chronically treated PD develop levodopa dose-responsive depression and hypomania (Damásio et al. 1971; Goodwin 1990; Hardie et al. 1984; Keshavan et al. 1986; Lees 1989; Maricle et al. 1995a,b, 1998; Nissenbaum et al. 1987; Riley and Lang 1993). If these mood fluctuations prove to be primarily mediated by D1 receptors, this may suggest alternative treatment strategies for PD patients with these disabling symptoms.

The specific mechanism producing the D1 agonist-mediated response in STS is unclear. Previous rat studies do not provide many clues. Lateral temporal cortex appears to contain higher levels of D3 mRNA in primates than in rodents, but primate lateral temporal cortex expresses D1-like receptor protein at relatively low levels (Jackson and Westlind-Danielsson 1994; Levey et al. 1993). Thus the large response observed here may not be attributable exclusively to effects on local cortical D1 receptors. Alternatively, the blood flow response may reflect increased firing of afferents projecting to STS. The specific D1-influenced projections that may mediate this response are not obvious. The receptor-rich basal ganglia project to inferotemporal cortex but not substantially to STS (Middleton and Strick 1996). Thalamic afferents to STS arise primarily from the medial pulvinar nucleus, although there is some sparse innervation from the dopamine-influenced mediiodorsal and ventroposterolateral nuclei (Yeterian and Pandya 1989). Many investigators consider the STS a sensory convergence area, receiving unimodal as well as polymodal and highly processed sensory afferents from lateral and ventral temporal lobe, amygdala, thalamus, and cortical sensory regions (Pandya and Seltzer 1982; Seltzer and Pandya 1994). One could speculate that the attention-enhancing effects of stimulants, which require D1 receptors for at least some physiological effects (Moratalla et al. 1996), occur in part via indirect dopaminergic modulation of the higher-order, polymodal sensory processing attributed to STS. Consistent with this speculation Fletcher et al. (1996) reported that the nonspecific dopamine agonist apomorphine modulates a CBF response in the STS to verbal tasks in patients with schizophrenia.

Decreases in rCBF

The CBF decreases in thalamus and pons are new findings. No significant effect on thalamic metabolism was seen in normal rats (Trugman and James 1993). However, a metabolic decrease in thalamus is consistent with activation via D1 receptors of striato-(internal)pallidal GABAergic neurons, causing a decrease in firing of pallidal afferents to thalamus (Young and Penney 1993). Rodent studies did not provide data for pons (Palacios and Wiederhold 1985; Trugman and James 1993).

The statistically most significant decrease, however, was centered in globus pallidus, pars externa (GP e). With the image resolution available with PET, we cannot tell whether this reflects a single response in GP e or two responses in flanking structures, such as putamen and globus pallidus, pars interna (GP i). SKF38393 had no significant net effect on GP 2DG metabolism in awake, normal rats (Engber et al. 1993; Trugman and James 1993), but responses in 6OHDA-lesioned animals were mixed (Wooten and Trugman 1989).

Differences from ex vivo rodent studies

Ex vivo 2DG studies in normal rats using acute doses of the D1 partial agonist SKF38393 have shown marked (22%) increases in metabolic activity in the substantia nigra pars reticulata (SNpr) and similar increases in the entopeduncular nucleus (EP), the rat homologue of the primate GP i. Metabolic decreases were seen in the lateral habenula (Trugman and James 1993). These responses are sensitive to functional status including induction of parkinsonism or treatment with dopaminergic agents (Engber et al. 1993; Morelli et al. 1993, 1995; Trugman and James 1992, 1993; Trugman and Wooten 1987; Trugman et al. 1989; Wooten and Trugman 1989).

In comparing these results with our data, there were interesting differences, most notably the prominence of the temporal lobe response in our primate model and the absence of increases in GP i and midbrain regions. There are several possible, nonexclusive, explanations for these differences.

Some of the differences between our data and the rodent 2DG results may be attributable to differences in technique. First, we measure blood flow rather than glucose metabolism so quantitative differences may be expected. Second, partial volume averaging (due to the lower resolution of PET compared with film autoradiography) reduces the peak magnitude of our signal. For instance, the GP i is small relative to the local density of dopamine receptors for at least some physiological effects (Moratalla et al. 1996), occur in part via indirect dopaminergic modulation of the higher-order, polymodal sensory processing attributed to STS. Consistent with this speculation Fletcher et al. (1996) reported that the nonspecific dopamine agonist apomorphine modulates a CBF response in the STS to verbal tasks in patients with schizophrenia.
image resolutions that raise similar issues, and rCBF increases of 6–17% are generally considered quite substantial. Third, we studied normal animals; in rodent studies, the responses to DA agonists are much smaller in magnitude in normal animals than in lesioned animals. Fourth, the limited number of available subjects may have decreased our power to replicate some of the activations reported from ex vivo autoradiographic studies in rats.

Conceivably N2O anesthesia could account for differences in our results, but several lines of evidence suggest this is unlikely. Direct effects of inhaled N2O on rCBF are irrelevant to interpreting this study since N2O concentration remained constant throughout the study. More importantly, under N2O anesthesia, rCBF responses to pCO2 changes or certain behavioral or pharmacologic stimuli remain intact (Fox et al. 1992; Yaster et al. 1994), and in studies with the D2-like agonist quinpirole, we demonstrated identical pallidal rCBF responses in N2O-sedated baboons and in awake nemestrina monkeys (Perlmutter et al. 1993). Furthermore although the anesthetic effects of N2O appear to be mediated through N-methyl-D-aspartate (NMDA) receptor blockade (Jevtovic-Todorovic et al. 1998), the NMDA antagonist MK801 does not interfere with the coupling of metabolism and blood flow (Nehls et al. 1990) and produces only modest effects on D1-agonist-induced changes in behavior or metabolism (Engber et al. 1993). Observations such as these contributed to our choice of N2O anesthesia for this study.

However, it remains possible that animals sedated with N2O have different physiologic responses to dopaminergic agents compared with awake animals. This would not be unprecedented since chloral hydrate, halothane, or barbiturate anesthesia substantially alters the regional metabolic response to dopamine agonists (Grome and McCulloch 1981, 1983), and nitrous oxide may affect cerebral metabolic responses to some physiologic stimuli (Crosby et al. 1983). In support of this possibility, we have recently found that an acute dose of levodopa causes decreased putaminal rCBF in sedated baboons but increased putaminal rCBF in awake humans or an awake monkey (Hershey et al. 1997). Nevertheless as noted in the preceding text, there was an rCBF increase in amygdala in all of these models, suggesting that at least the amygdala activation reported here is not due to the effects of nitrous oxide.

Finally, we have assumed that the rCBF changes reflect changes in neuronal firing. Since SKF82958 had no effect on absolute global blood flow, the alternative would be to posit that the drug directly dilated blood vessels in some brain regions and constricted vessels in other regions. Such effects were not typical of studies with other dopaminometrics (Azuma et al. 1988; McCulloch and Harper 1977). McCulloch, Kelly and Ford (1982a) measured changes in regional blood flow and metabolism induced by apomorphine and showed that after accounting for the drug’s effects on global blood flow, residual regional variations were attributable to changes in neuronal metabolism. Thus it is reasonable to assume that the observed regional CBF responses faithfully reflect regional metabolic changes although we have not directly tested this assumption with SKF82958.

Despite these caveats, we believe the differences in our results in baboons compared with those reported in rodents are likely meaningful rather than artifactual. In the resting state regional brain metabolism is similar in rodents and primates (Blin et al. 1991). This suggests that different metabolic or rCBF responses to a physiologic stimulus indicate true differences in the sensitivity of the physiologic system probed rather than differences in baseline activity. There are well-known differences in basal ganglia anatomy and pharmacology between rodents and primates (Jackson and Westlind-Danielsson 1994; Parent 1990; Pif et al. 1991), and the prominent temporal lobe activation in primates may reflect such differences.

**Spatial averaging of functional imaging data in nonhuman species**

In addition to the physiological implications of this study for dopaminergic function, its methodological implications should also be mentioned. Among the technical advances in the development of functional neuroimaging, one important early step was the development of methods to combine data from different subjects in a common atlas space (Fox et al. 1985, 1988). This allowed greater sensitivity to low-magnitude responses and reduction in individual anatomic variation (Fox et al. 1988; Raichle et al. 1991). Although nonhuman species have been crucial to the development of many widely used functional imaging methods (Perlmutter et al. 1989, 1991; Raichle et al. 1983; Schwartz et al. 1979), intersubject image averaging in a common atlas space has never been applied to functional imaging in a nonhuman species. In part this may be attributed to the appropriate use of humans for many studies of cognition, emotion, and sensorimotor function. However, other species may be more appropriate for some purposes, such as longitudinal study of lesion models of human disease (Perlmutter et al. 1997), neuropharmacologic investigations (Black et al. 1997a), or drug development (Perlmutter 1995). In this study we provide an example of such an application by applying an experimental drug to probe the dopaminergic system, using intersubject averaging of baboon PET images to increase sensitivity and reduce noise.

Atlas methods have been used for years to aid in identifying individual regions of interest in individual animals studied with specific radioligands (e.g., Perlmutter et al. 1989). However, for functional activation studies, investigators have resorted to using a priori-defined regions of interest in each animal rather than examining data from the entire brain (e.g., Black et al. 1997a; Tsukada et al. 1997). Tsujimoto et al. (1997) averaged PET data from two macaques after scanning each animal with the canthomeatal line placed along the center plane of the scanner, but no spatial normalization was performed to account for differences in brain size. However, we now report the use of a stereotactic method of spatial signal averaging across subjects in a nonhuman functional neuroimaging study. Further refinements are likely now that high-quality three-dimensional atlases are available for the macaque (Cannestra et al. 1997; Martin and Bowden 1996), and functional magnetic resonance imaging has been demonstrated in nonhuman primates (Logothetis et al. 1999; Stefanacci et al. 1998). A recent functional MRI study averaged functional responses to levodopa across several rhesus monkeys; however, details of the stereotactic method were not provided and the analysis was primarily region-based (Chen et al. 1999).

In summary, the implementation in nonhuman primates of a method for averaging PET responses across subjects allowed us to map physiologic responses to a dopamine D1 agonist in
vivo. The results, including the prominence of temporal lobe responses, were not predicted by prior reports in rodents but confirm and extend our reports of the rCBF effects of levodopa in both humans and nonhuman primates.

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D₂ AGONIST ACTIVATES TEMPORAL LOBE IN PRIMATES


