Dopamine is released in the striatum during human emotional processing

Rajendra D. Badgaiyan[a,b]

As the role of dopamine in human emotional processing is unclear, we used a dynamic molecular imaging technique to examine whether striatal dopamine is released during processing of negative emotions in healthy volunteers. After volunteers have received an intravenous injection of a dopamine receptor ligand ^{11}C-raclopride, they were asked to perform a task that elicited negative emotions. During task performance the ligand concentration was measured dynamically using a positron emission tomography camera. Analysis of the data indicated that the task performance is associated with dopamine release in the head of caudate and in the dorsal putamen bilaterally. *NeuroReport* **21:1172–1176 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

NeuroReport 2010, **21**:1172–1176

Keywords: caudate, dopamine, emotion, molecular imaging, negative emotion, positron emission tomography, putamen, raclopride, striatum

[a]Department of Psychiatry, University at Buffalo, New York and [b]Division of Nuclear Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Dr Rajendra D. Badgaiyan, MD, SUNY at Buffalo, 105 Parker Hall, University at Buffalo, Buffalo, NY 14214, USA
Tel/fax: +1 716 580 3063; e-mail: rbrb@buffalo.edu

Received 21 September 2010 **accepted** 29 September 2010

Introduction

We have observed earlier that dopamine is released in a number of brain areas outside the striatum during processing of negative emotions in healthy volunteers [1]. On account of methodological constraints (described later), dopamine released in the striatum could not be detected in this study. As a result, an important aspect of dopaminergic control of human emotion remains uninvestigated. Evidence from both, animal and human experiments suggests that striatal dopamine is critically involved in emotional processing. Neuroimaging studies have reported increased activation both in the dorsal [2] and the ventral [3,4] striatum and in animals, changes in emotional responses are observed after activation of the striatal dopaminergic system [5].

Disrupted emotional processing in patients with Parkinson's disease [6] also indicates involvement of striatal dopamine. On account of this involvement activations are observed in the basal ganglia of healthy volunteers during emotional processing [2,7]. Animal experiments provide stronger evidence of striatal dopaminergic processing. Thus, it was shown that electrical stimulation of the ventral tegmental nucleus increases dopamine release and produces fear reactions in cats [8]. A neurotoxic lesion in this area causes attenuation of fear responses [9]. Further, conditioned fear responses are disrupted when dopaminergic neurons of the nucleus accumbens (NAc) are inactivated [5] and microinjection of a dopaminergic agent in the rat NAc elicits the 50-kHz ultrasonic vocalization, which is a measure of pleasure in these animals [10].

As evidence of dopamine processing came mostly from animal experiments that used conditioned responses, the validity of these data in humans is controversial [11] because human emotions are dependent more on cultural and cognitive inputs [12] rather than conditioning [11]. It is possible that the human brain uses a different processing strategy than the laboratory animals. Probably because of this difference, activation in the ventral striatum is not observed in healthy volunteers during processing of negative emotions [2,7], even though involvement of this area in animals has been shown in a number of experiments [8]. There is, therefore, a need to examine the role of striatal dopamine in the processing of human emotions.

In this experiment we used a dynamic molecular imaging technique to detect, map, and measure striatal dopamine released during processing of negative emotions in healthy volunteers. Earlier, this technique was used to detect dopamine released in the striatum during performance of a number of cognitive and behavioral tasks [13–16]. Using a variant of this technique, we recently detected dopamine released outside the striatum during emotional processing [1]. In the variant technique task-induced release of dopamine was detected using a high-affinity dopamine receptor ligand ^{18}F-fallypride. Owing to its high affinity, this ligand is ideal for the detection of dopamine released outside the striatum where receptor density is low. It, however, takes several hours to bind to the receptors in high receptor density areas (the striatum). Therefore, we could not detect striatal dopamine released during emotional processing [1]. In the current experiment instead of ^{18}F-fallypride, a relatively low-affinity ligand ^{11}C-raclopride was used. This ligand binds to available striatal receptors within a few minutes. However, in the low receptor density areas outside the striatum, ^{11}C-raclopride does not bind in detectable quantity. This ligand, therefore, is used for the

0959-4965 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/WNR.0b013e3283410955

detection of striatal dopamine released in response to pharmacological and cognitive challenges [13–16]. In this experiment the ligand ^{11}C-raclopride was used to detect, map, and measure striatal dopamine released during processing of negative emotions in healthy volunteers.

Materials and methods

The study was conducted on healthy right-handed native English speaking volunteers (four males, four female; mean age 27.7 years) who had no history of a psychiatric or neurological disorder. The study protocol and consent forms were approved by the Institutional Review Board of Massachusetts General Hospital (Partner's Healthcare), Boston.

Dopamine released in the striatum during emotional processing was detected and mapped using a dynamic molecular imaging technique. In this technique a radiolabeled ligand is administered before task performance. The ligand concentration is dynamically measured during the experiment using a positron emission tomography (PET) camera to estimate the rate of its displacement from the dopamine receptor sites. As the ligand competes with endogenous dopamine for occupancy of receptor sites, it is displaced at a higher rate in the areas in which dopamine is released during task performance. The scan procedures used in this experiment followed the protocol described in our earlier publications [1,14–17] and outlined briefly in the following paragraphs.

After volunteers were positioned in the PET camera, their heads were fixed using an air-lock pillow. A neuroshield was placed between the head and the body to reduce the detection of scattered photons. Thereafter, each volunteer received an intravenous bolus (10–15 mCi; mean 13.73 mCi) of a dopamine receptor ligand, ^{11}C-raclopride, at a high specific activity (mean specific activity 1114 mCi/μM). Immediately after the injection, an emotional task (described below) and the PET data acquisition started.

The emotional task was similar to the one we used to study extrastriatal dopamine in an earlier experiment [1]. It consisted of a control and a test condition. In the control condition the volunteers were shown a list of emotionally neutral words (e.g. park, pencil) and were asked to indicate the intensity of emotion elicited by each word in a scale of 1–3 (1 = no emotion; 3 = intense emotional arousal). At 25 min after the ligand injection, unbeknownst to the volunteers, the task was changed from the control to the test condition. In the test condition neutral words were replaced by negative emotional words (e.g. fire, blood). In both conditions stimuli were presented for 4500 ms. It was followed by a cross mark (500 ms). A total of 200 neutral and an equal number of emotional words were used in the experiment. During the experiment ligand concentration was measured in 30-s epochs in the first 5 min and then at 60-s epochs, using an ECAT EXACT HR + PET camera (Siemens Medical Solutions, Pennsylvania, USA) operating in three-dimensional mode.

The dynamic molecular imaging technique used in this experiment exploited the competition between the ligand ^{11}C-raclopride and endogenous dopamine for occupancy of the same receptor-binding sites. On account of this competition, dopamine released during task performance displaced the ligand from the receptor sites. The rate of ligand displacement therefore increased in the brain areas in which dopamine was released during task performance. We estimated the rate of displacement by dynamically measuring ligand concentration and applying the data to a receptor kinetic model developed for this purpose [17].

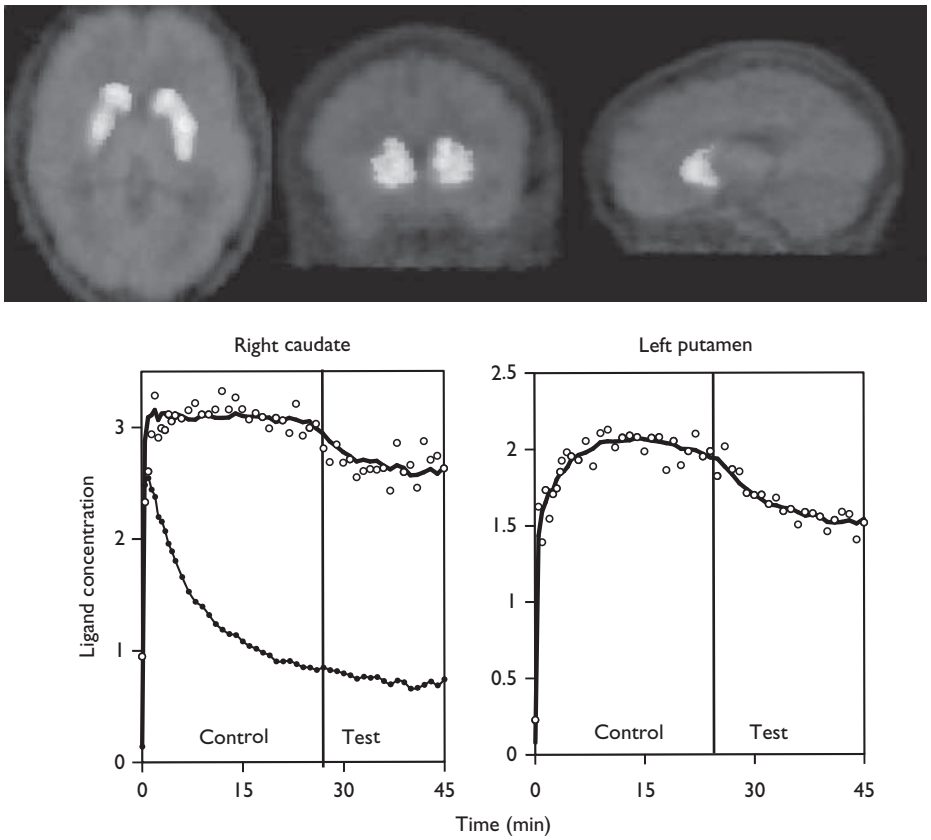
PET data analyses

Procedures used for the analyses of PET data were essentially similar to those used in earlier studies [1,14–17]. Briefly, the images were reconstructed as $128 \times 128 \times 63$ element volumes using a standard three-dimensional filtered back projection algorithm with corrections for photon attenuation, random coincidences, scatter, and dead time. Thereafter, the images were registered to align each frame to a common orientation, using the following procedure: first, all frames were smoothed with a 5-mm full-width half-maximum Gaussian filter; then variation in spatiotemporal distribution was corrected by registration of temporally adjacent frames and finally, using a transformation matrix, all frames were aligned to a reference frame. Thereafter, a voxel wise analysis of data was carried out on each volunteer using a kinetic model that was developed to detect transient changes in ligand displacement. Using this model, quantitative maps of kinetic parameters were generated for each volunteer. These data were then pooled to acquire cohort means and variances. The pooling involved elastic registration of the sum of image data of each volunteer to a standard template, using statistical parametric mapping software, SPM99 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) [18]. All images were normalized to a stereotactic template. This transformation was applied to the entire dynamic sequence to allow further analysis in the stereotactic space. A voxel-wise t map was then computed to localize voxels in which the rate of ligand displacement increased significantly after task initiation. Finally, time–activity curves were drawn for the voxels showing maximum ligand displacement. The cerebellum was used as a reference region (because of paucity of dopamine receptors), and a time–activity curve for this region was also drawn to estimate clearance rate of free and nonspecifically bound ligand.

Results

The emotional words presented in the test condition elicited significantly ($P < 0.001$) stronger emotion than the words shown in the control. Mean emotional ratings

Fig. 1



t Map showing areas of the striatum in which the rate of ligand (^{11}C-raclopride) displacement increased significantly ($t>3$) after initiation of a task that elicited negative emotion (vertical line). The time–activity curves show the concentration history and least square fits for the ligand in activated regions of the right caudate and left putamen. The lower curve in the left panel represents concentration history in the reference region (cerebellum) in which the rate of ligand displacement did not change significantly after task initiation.

(1 = no emotion; 3 = intense emotional arousal) in the control and test conditions were 1.29 ± 0.19 and 2.15 ± 0.52 respectively. There was no significant difference in the mean response time in the control (1654 ± 207 ms) and test (1581 ± 190 ms) conditions. Questionnaires filled in the debriefing confirmed that the words in the test condition elicited negative emotions and that there was a perceptible difference in state of emotional arousal in the control and test condition.

The PET data were analyzed using linear extension of simplified reference region model [17]. Using this model we computed t values of the difference in the rate before and after task initiation. The rate increased significantly in a number of striatal areas. The group mean of t values pooled across volunteers was significant ($t > 3.0$) bilaterally in the head of caudate and in the middle of dorsal putamen, indicating dopamine release in these areas during task performance. The maximum t values measured in a voxel in the 'activated' areas were 3.43 and 4.03 in the left and right caudate; and 4.03 and 3.6 in the left and right putamen respectively. Approximate Talairach coordinates of the voxels that had maximum t values were (x, y, z) 10, 16, 6 and −12, 15, 10 for the caudate and 17, 8, −4 and −22, −4, 6 for the putamen activation (Fig. 1). We also estimated the ligand binding potential during the experiment at each of the activated voxels. The mean binding potential estimated in the right and left caudate were 2.3 and 2.2 respectively. It was 1.8 in the right putamen and 1.9 in the left putamen. We did not find significant task-induced changes in the rate of ligand displacement in the reference region – cerebellum. This indicates that the changes observed in the striatum were because of the ligand displacement elicited by task-induced release of striatal dopamine.

Discussion

The results of this experiment complement and extend our earlier observation of increased dopamine release in the amygdala, prefrontal cortex, and medial temporal lobe during processing of negative emotions in healthy volunteers [1]. The findings of dopamine release in the

dorsal striatum (caudate and putamen) is consistent with the observation of increased regional cerebral blood flow in this area during the processing of self-generated negative emotion of sadness [2] and transiently elicited sadness [7]. It seems that the increased blood flow observed in these experiments was because of increased activity of the striatal dopamine system.

As dopamine release in the mid-dorsal putamen is associated primarily with motor planning [14–16], its activation in the current experiment could be related to the planning and execution of emotional motor response (e.g. facial, autonomic). Dopamine of the caudate is associated with processing of motor memory [14,15] and reward [13] in human and with encoding of fear-related stimuli [19] in animals. As memories of past experiences and reward potentials of the stimuli determine their affective values, the caudate activation observed in this experiment could be associated with the assignment of these values. The dopamine system of the caudate is uniquely suited for this role because it receives input from the orbitofrontal cortex in which the valences of the emotional stimuli are processed [20].

In animals, dopamine of the dorsal striatum has a limited role in emotional processing. Most animal studies have implicated the ventral striatum. Thus, stimulation of the ventral tegmental nucleus elicits fear response in cats and a neurotoxic lesion in this area attenuates fear [9]. Similarly, inactivation of the NAc impairs conditioned fear response [5]. In animals, NAc is involved in processing of positive emotions also. Thus, enhanced dopamine efflux from this nucleus is observed when animals receive food reward [21] and intranuclear injection of a dopaminergic agent in the rat elicits the 50-kHz ultrasonic vocalization, which is a measure of pleasure in these animals [10].

In this experiment dopamine was released in the dorsal striatum, not in the ventral striatum. It suggests that dopamine processing of human and animal emotions is not identical. Although in animals both positive and negative emotions are processed in the ventral striatum, human striatum seems to make a distinction between the two types of emotions. The ventral striatum processes only positive emotions and negative emotions are processed in the dorsal striatum. This distinction is consistent with the observations of neuroimaging experiments. These experiments have reported ventral striatal activation during presentation of pleasant music [3], positive words [4], and financial reward [22]. In contrast, negative emotional stimuli do not activate the ventral striatum. Most of these stimuli activate dorsal striatal structures (mostly the caudate). Thus, the dorsal striatum is activated during self-generated sadness [2], transiently elicited sadness [7], and financial penalties [22].

It is therefore not surprising that negative emotional stimuli did not release dopamine in the ventral striatum in this experiment. This finding is consistent with clinical observation in patients in early stages of Parkinson's disease, who have difficulty in processing the negative but not positive emotions [6]. As dopamine is depleted only in the dorsal striatum in early stages, it suggests that negative emotions are processed in the dorsal striatum. This discussion on differences in the activity patterns in the human and animals brains assumes that the reliability of human data acquired using neuroimaging and molecular imaging techniques is comparable with the animal data obtained using more invasive procedures.

The findings of this experiment extend and complement our earlier observation of increased dopamine release in the amygdala, prefrontal and medial temporal areas during processing of negative emotions [1]. Taken together, it seems that the dopamine system of these extrastriatal structures communicate with the striatal system during emotional processing. Anatomically, these structures are connected not only with the dopaminergic pathways that project to the striatum (nigrostriatal), amygdala, hippocampus (mesolimbic), and prefrontal cortex (mesocortical); but also by direct neural connections. Thus, the amygdala is connected to the dorsal striatum by amygdalo-striatal pathway that originates in the central nucleus of amygdala and through the synaptic relay in the substantia nigra pars compacta, terminates in the striatum [23]. The striatum and prefrontal cortex are connected through dopaminergic striatofrontal projections. Further, the evidence suggests that the hippocampus, striatum, and amygdala are interconnected through dopamine-dependent neural connections [24].

Conclusion

The results of this experiment indicate that the dorsal striatal dopamine system is involved in the processing of negative human emotions. This is in contrast with the findings in animals in which the ventral striatal dopamine system processes both, the negative and positive emotions. Human and animal emotions are therefore, processed differently by the dopamine system. These findings suggest that the impaired emotional processing observed in psychiatric (e.g. posttraumatic stress disorder, schizophrenia) and neuropsychiatric (e.g. Parkinson's disease) conditions could be because of dysregulated dopamine neurotransmission.

Acknowledgements

The study was supported by NIH (1R21MH073624 and 1R21MH079435) grant, Dana Foundation, and Shriners Hospital for Children.

References

1 Badgaiyan R, Fischman A, Alpert N. Dopamine release during human emotional processing. *Neuroimage* 2009; **47**:2041–2045.

2 Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, *et al.* Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat Neurosci* 2000; **3**:1049–1056.

3 Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci U S A* 2001; **98**:11818–11823.

4 Hamann S, Mao H. Positive and negative emotional verbal stimuli elicit activity in the left amygdala. *Neuroreport* 2002; **13**:15–19.

5 Haralambous T, Westbrook RF. An infusion of bupivacaine into the nucleus accumbens disrupts the acquisition but not the expression of contextual fear conditioning. *Behav Neurosci* 1999; **113**:925–940.

6 Dara C, Monetta L, Pell MD. Vocal emotion processing in Parkinson's disease: reduced sensitivity to negative emotions. *Brain Res* 2008; **1188**:100–111.

7 George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM. Brain activity during transient sadness and happiness in healthy women. *Am J Psychiatry* 1995; **152**:341–351.

8 Levita L, Dalley JW, Robbins TW. Nucleus accumbens dopamine and learned fear revisited: a review and some new findings. *Behav Brain Res* 2002; **137**:115–127.

9 Levita L, Dalley JW, Robbins TW. Disruption of Pavlovian contextual conditioning by excitotoxic lesions of the nucleus accumbens core. *Behav Neurosci* 2002; **116**:539–552.

10 Burgdorf J, Wood PL, Kroes RA, Moskal JR, Panksepp J. Neurobiology of 50-kHz ultrasonic vocalizations in rats: electrode mapping, lesion, and pharmacology studies. *Behav Brain Res* 2007; **182**:274–283.

11 Burgdorf J, Panksepp J. The neurobiology of positive emotions. *Neurosci Biobehav Rev* 2006; **30**:173–187.

12 Paul ES, Harding EJ, Mendl M. Measuring emotional processes in animals: the utility of a cognitive approach. *Neurosci Biobehav Rev* 2005; **29**:469–491.

13 Pappata S, Dehaene S, Poline JB, Gregoire MC, Jobert A, Delforge J, *et al.* In vivo detection of striatal dopamine release during reward: a PET study with [(11)C]raclopride and a single dynamic scan approach. *Neuroimage* 2002; **16**:1015–1027.

14 Badgaiyan RD, Fischman AJ, Alpert NM. Explicit motor memory activates the striatal dopamine system. *Neuroreport* 2008; **19**:409–412.

15 Badgaiyan RD, Fischman AJ, Alpert NM. Striatal dopamine release in sequential learning. *Neuroimage* 2007; **38**:549–556.

16 Badgaiyan RD, Fischman AJ, Alpert NM. Striatal dopamine release during unrewarded motor task in human volunteers. *Neuroreport* 2003; **14**:1421–1424.

17 Alpert NM, Badgaiyan RD, Livini E, Fischman AJ. A novel method for noninvasive detection of neuromodulatory changes in specific neurotransmitter systems. *Neuroimage* 2003; **19**:1049–1060.

18 Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general approach. *Hum Brain Mapp* 1995; **2**:189–210.

19 White NM. Effect of nigrostriatal dopamine depletion on the post-training, memory-improving action of amphetamine. *Life Sci* 1988; **43**:7–12.

20 Smith AP, Henson RN, Dolan RJ, Rugg MD. fMRI correlates of the episodic retrieval of emotional contexts. *Neuroimage* 2004; **22**:868–878.

21 Ahn S, Phillips AG. Dopamine efflux in the nucleus accumbens during within-session extinction, outcome-dependent, and habit-based instrumental responding for food reward. *Psychopharmacology (Berl)* 2007; **191**:641–651.

22 Elliott R, Friston KJ, Dolan RJ. Dissociable neural responses in human reward systems. *J Neurosci* 2000; **20**:6159–6165.

23 Ferreira TL, Shammah-Lagnado SJ, Bueno OF, Moreira KM, Fornari RV, Oliveira MG. The indirect amygdala-dorsal striatum pathway mediates conditioned freezing: insights on emotional memory networks. *Neuroscience* 2008; **153**:84–94.

24 Okubo Y, Olsson H, Ito H, Lofti M, Suhara T, Halldin C, *et al.* PET mapping of extrastriatal D2-like dopamine receptors in the human brain using an anatomic standardization technique and [^{11}C]FLB 457. *Neuroimage* 1999; **10**:666–674.