Neurotransmitter Imaging: Basic Concepts and Future Perspectives

Rajendra D. Badgaiyan*

Department of Psychiatry, SUNY at Buffalo, NY 14214; Harvard University, Cambridge, MA 02138, USA

Abstract: Neurochemistry of human cognition remains uninvestigated because neuroimaging techniques have limited ability to detect neurochemical changes associated with cognitive processing. In recent years investigators have used molecular imaging to develop methods for detection, mapping and measurement of neurotransmitters released acutely during cognitive processing in the live human brain. Most of these methods exploit the competition between endogenous neurotransmitter and a radiolabeled receptor ligand. Because of the competition, the ligand concentration decreasesin the brain areas where neurotransmitter is released endogenously during a task performance. The decreased concentration is detected by measuring the activity of intravenously injected radioligand using a PET camera. The PET data acquired dynamically isapplied to a receptor kinetic model, which estimates kinetic parameter values at multiple time point. Based on these values dopamine released during performance of a task is detected, mapped and measured. By using different ligands, dopamine released inside or outside the striatum can be detected using this technique. The neurotransmitter imaging technique at present can detect acute changes only in dopamine neurotransmission. Since it significantly limits the scope, there is a need to develop methods and ligands for detection of acute changes in the levels of other neurochemicals.

Keywords: Molecular imaging, raclopride, fallypride, neurochemistry of cognition, dopamine.

Since neuroimaging techniques have limited ability to detect changes in neurochemistry,there is an abundance of anatomical data but relatively little information on neurochemical changes associated with cognitive processing. Lack of data on the chemical control of human cognition has significantly impacted our understanding of cognitive processes, particularly because neurotransmitters have strong regulatory influence. Our understanding of human cognition will therefore remain incomplete until a reliable method to detect of neurochemical changes associated with cognitive processing is developed.

In recent years investigators have developed a number of methods to detect acute changes in neurotransmission. Most of these methods are based on molecular imaging techniques, which were used in the past to study chronic changes in conditions like Alzheimer's disease [1-3] Parkinson's disease [1, 4-6] disease and drug addiction [7-12]. In these studieschanges in receptor kinetic parameters were detected by administering a radiolabeled ligand and measuring its concentration by positron emission tomography (PET) or single photon emission computed tomography (SPECT) camera. Since a ligand binds to the receptors that are not occupied by its neurotransmitter, the amount of ligand binding is proportional to the number of unoccupied receptors. This relationship is exploited by the receptor kinetic models, for quantitativemeasurement of receptor kinetic parameters. The measurement essentially involves transformation of the ligand concentration to the number of receptors occupied by a neurotransmitter.

The ligand concentration acquired using the PET or SPECT, represents the amount of ligand bound to specific receptors (specific binding) as well as the amount dissolved in the blood or bound to the plasma or tissue proteins (nonspecific binding). Since the ligand that is bound only to the receptors compete with endogenous neurotransmitter, it is necessary to measure the amount of ligand that is specifically bound to receptors. It requires isolation of specific binding from the total ligand concentration measured in the brain (Fig. **1**).

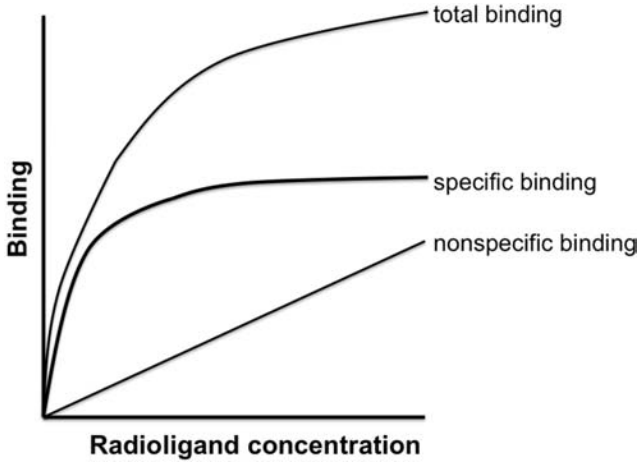

Fig. (1). Saturation binding experiment: Ligand bound to the receptors (specific binding) is estimated by subtracting the amount of ligand dissolved in arterial blood from total binding measured in saturation binding experiments (see text for details).

For isolation of specific binding, investigators have developed a number of kinetic models. These models explain how the ligand is distributed in the brain after intravenous administration. The most commonly used model (three-compartment model) assumes that it distributes in three compartments (Fig. **2**): the plasma compartment (in the arterial blood); the nondisplaceable compartment (free and non-

*Address correspondence to this author at the 105 Parker Hall, University at Buffalo, Buffalo, NY 14214, USA; Tel: 716-580-3063; Fax: 716-580-3063; E-mail: rbrb@buffalo.edu

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Fig. (2). Three-compartment model: The model explains dynamics of ligand distribution in the brain.

specifically bound ligand); and the receptor compartment (bound to the receptors). The nondisplaceable compartment consists of structures outside the receptor and includes the ligand dissolved in plasma and bound nonspecifically to the plasma or tissue proteins. According to this model the ligand concentration in the receptor compartment (specific binding) can be measured by subtracting its concentration in the plasma and nondisplaceable compartments from the total concentration. The model assumes a positive gradient between the plasma and tissue concentration of ligand, in the period immediately following intravenous injection. The gradient allows the ligand to move from the plasma to nondisplaceable and receptor compartments. It further assumes that theory of mass action explains the flow of ligand between different compartments. Thus, at equilibrium same amount of ligand flows in either direction, therefore, K1 equals k2, and k3 equals k4. Ultimately K1 equals k4 (see Fig. **2**). At this steady state, specific binding (B) can be measured using Michaelis-Menton equation. The equation however requires values of the maximum number of receptors available to the ligand (Bmax), the concentration of free ligand (F), and equilibrium dissociation constant of the ligand (Kd). The dissociation constant Kd is the ratio of rates at which the ligand associates (K_{on}) and dissociates (K_{off}) from receptor sites, and it is defined as the concentration of ligand (expressed in units of moles/liter) that occupies half of the available receptors at equilibrium as shown in Fig. (**3**). The Michaelis-Menton equation describes the relationship between these values as follows:

$$B = \frac{Bmax * F}{Kd + F}$$

In molecular imaging studies a small amount (tracer dose) of ligand is administered to avoid pharmacological effect. Since ligands are either agonists or antagonists of the neurotransmitter receptor, at a higher dose these substrates alter neurotransmitter activity. Because small amount of ligand yields a very small value of F, this parameter is disregarded in the denominator of the above formula to get the following simplified formula:

$$B = \frac{Bmax * F}{Kd}$$

Thus, specific binding can be estimated if Bmax, Kd and F are known. Since ligands are freely diffusible across blood brain barrier; at equilibrium its arterial blood concentration equals the free ligand concentration in the brain (F). Thus, the value of F can be determined by measuring the arterial concentration. The arterial concentration can also be used to measure the other two parameters: Bmax and Kd. The measurement involves a saturation binding experiment in which total and the arterial concentration of the ligand are measured after different doses of ligand are administered (Fig. **1**). To measure specific binding in these experiments, the arterial concentration is subtracted from the total binding. These values are then plotted on a graph to estimate Bmax and Kd using nonlinear regression as shown in Fig. (**3**). Once all 3 values (Bmax, Kd and F) are available, specific binding is calculated using the above formula.

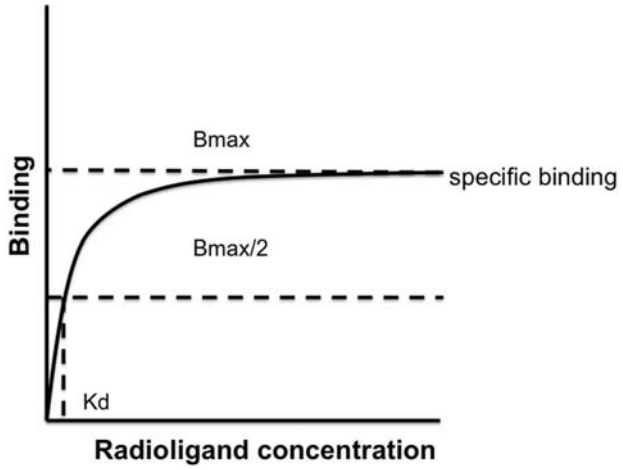

Fig. (3). Bmax and Kd: Using data acquired in saturation binding experiments, Bmax and Kd can be estimated by plotting a regression graph between the binding and ligand concentration.

In molecular imaging experiments specific binding is generally expressed in terms of binding potential (BP), which is the ratio ofspecific binding (B) and free ligand (F):

$$BP = B / F$$

After substituting value of B (Bmax*F/Kd) derived above, the equation is re-written as follows:

$$BP = \frac{B}{F} = \frac{Bmax}{Kd}$$

Thus, BP is defined as the ratio of maximum number of available receptors and dissociation constant of the ligand at equilibrium. Affinity of the ligand for larger receptor population or smaller dissociation constant therefore increases the ligand BP. Conversely a reduction in the number of receptors available to the ligand to bind (either because of reduced receptor density or increased neurotransmitter occupancy) decreases the BP. Because of its dependency on a number of variables, the BP is considered a sensitive index of changes in the status of neurotransmission.

Measurement of the BP using the above equation requires collection of multiple arterial blood samples. It makes

the procedure highly invasive and unsuitable for routine study. This limitation was addressed by developing simplified reference tissue model- the SRTM [13.14]. In this model the ligand concentration in a region of interest (ROI) is compared with the concentration measured in a reference region. The reference region is assumed to have no receptor for the specific neurotransmitter (e.g. cerebellum in dopamine studies). The ligand concentration in this region therefore approximates the nonspecific binding. In this method specific binding in an ROI is estimated by subtracting the ligand binding of the reference region from the binding in the ROI.

The ability of SRTM to measure BP without arterial blood sample was exploited for detection of acute changes in dopamine neurotransmission induced by pharmacological, behavioral and cognitive challenges. A number of experiments have used this model to demonstrate that the BP of dopamine ligands raclopride [15-18] and fallypride [19-22] decreases significantly after acute administration of amphetamine. The SRTM was also used to demonstrate that dopamine is released in the striatum when volunteers play a video game [23]. In this experiment the BP measured while volunteers played the game was compared with that measured at rest. Lower BP during the play (as compared to the BP measured at rest) indicated dopamine release. This experiment required two scans to determine dopamine release. This requirement reduced the sensitivity of detection because changes in the baseline levels of dopamine in the two scans (rest and play) cannot be accounted for. This method is therefore not used for detection of relatively small amount of dopamine released during processing of a specific cognitive task [24, 25].

Small amount of dopamine released during cognitive processing can be detected accurately if all parameters are measured in a single scan session. Therefore, investigators proposed methods to measure changes in BP in a single scan session. Using one of these methods, BP measured during performance of a gambling task was compared with the simulated baseline BP which was computed using data obtained from another group of volunteers [26]. This method also did not improve the sensitivity of detection because it used data obtained from a different group of volunteers.

To accurately detect small amount of dopamine, it is necessary to measure the control and activation BP from the same volunteers in the same scan session. An experimental design that includes 2 conditions (control and activation) in the same scan session however is not consistent with the assumptions of SRTM. It assumes that a steady physiological state is maintained during the entire scan session. A change in the task condition violates this assumption. The model therefore cannot be used to measure BP in these experiments. This problem could be resolved if the data obtained during the scan are divided in two subsets, each corresponding to the data acquired during the control and activation condition [15]. Since steady physiological state is maintained within each condition, SRTM can be used to analyze each dataset separately. The divided datasets however, do not provide adequate information needed to estimate the BP. These datasets therefore, are reconstructed to obtain two complete sets: one set representing the control (non-activated) and the other representing test (activated) condition. The SRTM can now be applied to these datasets for estimation of the BP in each condition. A voxel-wise comparison of the BP measured in the two conditions allows detection and mapping of changes in induced by a cognitive or pharmacological intervention.

Using this approach, it was demonstrated that amphetamine decreases the BP of raclopride in non-human primates [15]. We used this approach to detect and map changes in the ligand BP in the human brain during processing of executive inhibition [27]. However, as discussed above, this approach requires reconstruction of data. This process requires a number of assumptions that can potentially introduce errors, particularly if a single algorithm is used to reconstruct data in all voxels, irrespective of their kinetic properties. These estimates therefore may not accurately measure changes induced by the intervention.

To resolve some of the above problems, we used a different approach to measure acute changes in dopamine neurotransmission [28, 29]. We modified the algorithm that SRTM uses to measure receptor kinetic parameters. The modified algorithm eliminated the assumption of steady state and allowed the model to accept changes in dissociation rate of ligand in response to an altered synaptic level of neurotransmitter. The modification involved introduction of a term $\gamma \cdot \exp(-\tau(t-T)) \cdot \nu(t-T)$ in the dissociation parameter of SRTM. In the modified algorithm γ represents the amplitude of ligand displacement, τ accounts for the initial burst release of dopamine, t denotes the measurement time, T is the time of change in neurotransmitter level, and ν is the unit step function. In this model the least squares fitting procedure on a voxel-by-voxel basis is used to estimate receptor binding parameters and γ. The modified model (linear extension of simplified reference region model; LE-SRRM) allows estimation of parameters that describe ligand transport and binding, and the time dependent effects elicited by the task. The differential equation describing the model for instantaneous concentration history of the ligand has the following form:

$$PET(t) - R - C_R(t) + k_2 \int_0^1 C_R(u)du - k_2 \int_0^1 PET(u)\,du - \gamma \int_0^1 \upsilon(u-T)e^{-\gamma(u-T)} PET(u)\,du$$

where, C_R is the concentration of radioligand in a region devoid of specific binding (reference region), PET is the concentration of radioligand in a voxel with specific binding, R is the ratio of transport rates for the binding and reference regions, k_2 describes the clearance of nonspecifically bound tracer from the voxel, and k_{2a} includes information about dissociation from the receptor, γ represents the amplitude of transient effects, t denotes the measurement time, T is the task initiation time and ν(u-T) is the unit step function.

Using this model we detected, mapped and measured dopamine released during performance of a number of cognitive and behavioral tasks. These tasks include, implicit and explicit motor memory [30, 31], emotional processing [32, 33], motor planning [29], executive inhibition [27], explicit memory and executive processing [34].

In these experiments volunteers (while positioned in the PET camera) received a single intravenous bolus of a spe-

cific dopamine receptor ligand at high specific activity. Immediately after the injection, the control condition of a cognitive task and the PET data acquisition at 30-60 sec intervals started. The control condition was administered for 20-25 min. Thereafter it was switched to the test condition (activation condition), which continued for another 10-30 min. In a series of experiments we evaluated sensitivity and specificity of the acquired using this approach. These experiments confirmed that the technique is sensitive and specific to the task-induced release of dopamine in the striatum [28, 29]. At this stage, it was not possible to detect dopamine outside the striatum because the ligand ^{11}C-raclopride used for the detection binds and displaces in detectable quantity only in the areas where the receptor density is high [15-18, 35]. Since it was a major limitation of the method we started looking for a ligand that can be detected in low receptor density areas.

It was found that the ligands that have high affinity for dopamine receptors bind in detectable quantity outside the striatum [36]. But endogenously released dopamine cannot physically displace a high affinity ligand from receptor sites. It however, does not mean that these ligands cannot be used to detect dopamine. In molecular imaging experiments ligands are probably never physically displaced by neurotransmitters. Since the ligand and neurotransmitter rapidly associate and dissociate with the receptors, additional dopamine released after an intervention always finds an unoccupied receptor [37]. Moreover, the ligand binding is based on the number of available unoccupied receptors and not on its physical displacement from receptor sites. Thus, irrespective of the affinity, neurotransmitter released following an intervention decreases ligand binding, by reducing number of unoccupied receptors. Experimental confirmation of this concept was obtained by showing that the binding of a high affinity ligand ^{18}F-fallypride reduces significantly after amphetamine is injected intravenously in animals and healthy volunteers [19-22].

This confirmation prompted us to use fallypride for detection of dopamine released outside the striatum. In a recent experiment [33] we found that the ligand displaces from receptor sites at a higher rate during emotional processing. The rate was significantly higher in the amygdala, hippocampus and prefrontal cortex. Since numerous earlier studies have implicated these areas in emotional processing, the experiment suggested that fallypride could be used to detect dopamine released acutely in extrastriatal areas. Recently, another laboratory used this ligand and our receptor kinetic model (LE-SRRM) to detect dopamine released in the thalamus during processing of an attentional task [38]. In the fallypride experiment the ligand saturated extrastriatal receptors within 10-15 after an intravenous injection. The receptors in the high-density striatal areas however do not saturate in a 50 min experiment. It takes several hours to saturate receptors in the striatum. Because of this reason, fallyprideis not a good ligand to study striatal dopamine, particularly because by the time it saturates striatal receptors, its extrastriatal concentration reduces to undetectable level.

These experiments demonstrate that dynamic molecular imaging methods can reliably detect and map dopamine released anywhere in the brain during a task performance. This measurement should provide critical information concerning nature of dysregulated neurotransmission in psychiatric and neurocognitive conditions.

Following is a brief description of dynamic molecular imaging experiments in which dopamine release was detected, mapped and measured in the striatal [32] and extrastriatal [33] areas during emotional processing in healthy volunteers and patients with posttraumatic stress disorder.

Detection of Striatal Dopamine

In this experiment [32] volunteers received an intravenous injection of the ligand ^{11}C-raclopride at high specific activity. Immediately after the injection an emotional task was initiated. The task consisted of a control and a test condition. In the control a list of emotionally neutral words (e.g., Park, Pencil) was shown and volunteers were asked to indicate the intensity of emotion elicited by each word in a scale of 1-3. After 25 min (test condition) neutral words were replaced by emotional words (e.g., Fire, Blood). In both conditions stimuli were presented for 4500 msec. During the experiment, PET data were acquired dynamically. Analysis of these data revealed that the rate of ligand displacement increased significantly in the head of caudate, and in the middle of putamen bilaterally during presentation of emotional stimuli (Fig. **4**). This result suggest that striatal dopamine is released during emotional processing and confirmed that changes in dopaminergic activity induced by emotional processing can be detected using dynamic molecular imaging method.

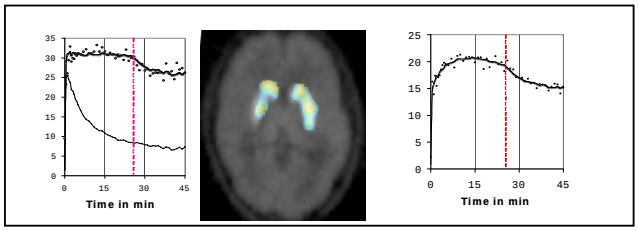

Fig. (4). Dopamine was released in the head of caudate (left panel) and middle of the putamen (right panel) bilaterally during emotional processing. Emotional task was initiated 25 min after the ligand injection (vertical line). The t-map (center) shows striatal area where significant change in the rate of ligand (^{11}C-raclopride) displacement was observed after task initiation. The rate did not change significantly in the reference region (lower curve in the left panel).

Detection of Dopamine Outside the Striatum

Since the ligand ^{11}C-raclopride cannot detect dopamine outside the striatum [15, 17, 18], in this experiment we used a high affinity dopamine receptor ligand ^{18}F-fallypride [33]. Immediately after the ligand injection the emotional task described above was administered. Analysis of PET data indicated significant increase in the rate of ligand displacement in extrastriatal areas that are implicated in emotional processing [39-44]. These areas included the amygdala, medial temporal lobe and ventral prefrontal cortex (Fig. **5**). Since we found dopamine release in the same extrastriatal areas that are implicated in emotional processing, the results demonstrate that ^{18}F-fallypride can be used to detect and map

dopamine released outside the striatum during task performance.

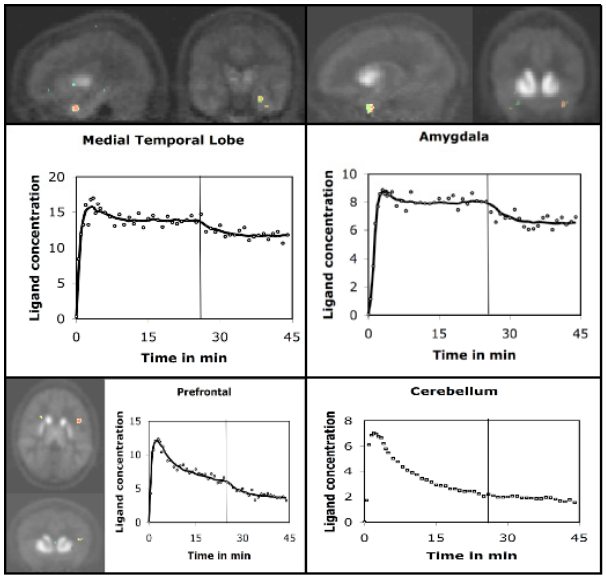

Fig. (5). The t-maps and time-activity curves show significant increase in the rate of ligand (^{18}F-fallypride) displacement after initiation of an emotional task. The increase was observed in the medial temporal lobe (top left), amygdala (top right), and inferior frontal gyrus (bottom left). The time-activity curves show the ligand concentration and least square fits (solid line) in the activated regions and in the cerebellum (bottom right), which was used as a reference region. The rate of displacement did not change significantly in the reference region after task initiation (vertical lines).

Group Differences

To examine whether dynamic molecular imaging can be used to detect changes in two groups of volunteer, we repeated the above experiment in patients with post-traumatic stress disorder (PTSD). Since emotional processing is impaired in these patients, we expected a different pattern of dopamine release. The preliminary results indicate that dopamine is released only in 2 striatal areas as opposed to 4 areas in healthy volunteers [32]. In addition to reduced number of activated area, the ligand BP was also lower in patients. These findings indicated reduced dopamine release in PTSD. This experiment demonstrated that dynamic molecular imaging method could be used to detect differences in dopamine neurotransmission in the two groups of volunteer.

Future Directions

The dynamic molecular imaging technique could be an important tool to study neurochemical changes associated with cognitive, affective and behavioral processing in healthy human brain and in psychiatric and neuropsychiatric conditions. Since the technique is currently at developmental stage, it can only be used to study dopamine neurotransmission. Future, because the brain processing involves multiple neurotransmitters and neuromodulators, it is important to develop and identify ligands that are suitable for detection of other neurochemicals.

The inability to simultaneously detect multiple neurotransmitters is another important limitation of the technique. Since most brain processes involve multiple neurotransmitters and neuromodulators, it is important for this technique to have the ability to detect multiple neurochemicals simultaneously. This will further enhance its utility in cognitive research. Another area that needs attention is enhancement of temporal resolution. If models and methods to detect temporal sequence of events are developed, the dynamic molecular imaging technique can be used to identify neural networks that process brain functions.

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REFERENCES

[1] Jacobs AH, Li H, Winkeler A, *et al.* PET-based molecular imaging in neuroscience. Eur J Nucl Med Mol Imaging 2003; 30(7): 1051-65.

[2] Wengenack TM, Jack CR, Jr., Garwood M, Poduslo JF. MR microimaging of amyloid plaques in Alzheimer's disease transgenic mice. Eur J Nucl Med Mol Imaging 2008; 35 Suppl 1: S82-8.

[3] Ryu E, Chen X. Development of Alzheimer's disease imaging agents for clinical studies. Front Biosci 2008; 13: 777-89.

[4] Elsinga P, Hatano K, Ishiwata K. PET tracers for imaging of the dopaminergic system. Curr Med Chem 2006; 13(18): 2139-53.

[5] Cropley V, Fujita M, Innis R, Nathan P. Molecular imaging of the dopaminergic system and its association with human cognitive function. Biol Psychiatry 2006; 59(10): 898-907.

[6] Casteels C, Vermaelen P, Nuyts J, *et al.* Construction and evaluation of multitracer small-animal PET probabilistic atlases for voxel-based functional mapping of the rat brain. J Nucl Med 2006; 47(11): 1858-66.

[7] Volkow ND, Wang GJ, Kollins SH, *et al.* Evaluating dopamine reward pathway in ADHD: clinical implications. Jama 2009; 302(10): 1084-91.

[8] Volkow N, Wang G, Telang F, *et al.* Dopamine increases in striatum do not elicit craving in cocaine abusers unless they are coupled with cocaine cues. Neuroimage 2008; 39(3): 1266-73.

[9] Volkow N, Wang G, Telang F, *et al.* Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J Neurosci 2006; 26(24): 6583-8.

[10] Iversen L. Neurotransmitter transporters and their impact on the development of psychopharmacology. Br J Pharmacol 2006; 147 Suppl 1: S82-8.

[11] Kimmel H, Ginsburg B, Howell L. Changes in extracellular dopamine during cocaine self-administration in squirrel monkeys. Synapse 2005; 56(3): 129-34.

[12] Fowler JS, Volkow ND, Ding YS, *et al.* Positron emission tomography studies of dopamine-enhancing drugs. J Clin Pharmacol 1999; Suppl: 13S-6S.

[13] Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. Neuroimage 1997; 6(4): 279-87.

[14] Lammertsma A, Hume S. Simplified reference tissue model for PET receptor studies. Neuroimage 1996; 4(3 Pt 1): 153-8.

[15] Zhou Y, Chen M, Endres C, *et al*. An extended simplified reference tissue model for the quantification of dynamic PET with amphetamine challenge. Neuroimage 2006; 33(2): 550-63.

[16] Martinez D, Slifstein M, Broft A, *et al*. Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. J Cereb Blood Flow Metab 2003; 23(3): 285-300.

[17] Laruelle M. Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. J Cereb Blood Flow Metab 2000; 20(3): 423-51.

[18] Dewey SL, Smith GS, Logan J, Brodie JD, Fowler JS, Wolf AP. Striatal binding of the PET ligand ^{11}C-raclopride is altered by drugs that modify synaptic dopamine levels. Synapse 1993; 13(4): 350-6.

[19] Cropley V, Innis R, Nathan P, *et al*. Small effect of dopamine release and no effect of dopamine depletion on [18F]fallypride binding in healthy humans. Synapse 2008; 62(6): 399-408.

[20] Riccardi P, Li R, Ansari M, *et al*. Amphetamine-induced displacement of [18F] fallypride in striatum and extrastriatal regions in humans. Neuropsychopharmacology 2006; 31(5): 1016-26.

[21] Mukherjee J, Christian BT, Narayanan TK, Shi B, Collins D. Measurement of d-amphetamine-induced effects on the binding of dopamine D-2/D-3 receptor radioligand, 18F-fallypride in extrastriatal brain regions in non-human primates using PET. Brain Res 2005; 1032(1-2): 77-84.

[22] Mukherjee J, Yang ZY, Lew R, *et al*. Evaluation of d-amphetamine effects on the binding of dopamine D-2 receptor radioligand, 18F-fallypride in nonhuman primates using positron emission tomography. Synapse 1997; 27(1): 1-13.

[23] Koepp MJ, Gunn RN, Lawrence AD, *et al*. Evidence for striatal dopamine release during a video game. Nature 1998; 393(6682): 266-8.

[24] Fischman AJ, Badgaiyan RD. Neurotransmitter Imaging. In: Charron M, editor. Pediatric PET. New York: Springer; 2006. p. 385-403.

[25] Fischman AJ, Badgaiyan RD. Functional imaging of neurotransmission. Current Medical Imaging Reviews. 2007; 3: 385-403.

[26] Pappata S, Dehaene S, Poline JB, *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(4): 1015-27.

[27] Badgaiyan RD, Wack D,. Release of Striatal dopamine during response inhibition. Society of Nuclear Medicine; 2011; San Antonio.

[28] Alpert NM, Badgaiyan RD, Livini E, Fischman AJ. A novel method for noninvasive detection of neuromodulatory changes in specific neurotransmitter systems. NeuroImage 2003; 19(3): 1049-60.

[29] Badgaiyan RD, Fischman AJ, Alpert NM. Striatal dopamine release during unrewarded motor task in human volunteers. Neuroreport 2003; 14(11): 1421-4.

[30] Badgaiyan RD, Fischman AJ, Alpert NM. Explicit Motor Memory Activates the Striatal Dopamine System. NeuroReport 2008; 19(4): 409-12.

[31] Badgaiyan RD, Fischman AJ, Alpert NM. Striatal dopamine release in sequential learning. NeuroImage 2007; 38(3): 549-56.

[32] Badgaiyan RD. Dopamine is released in the striatum during human emotional processing. NeuroReport 2010; 21: 1172-6.

[33] Badgaiyan RD, Fischman AJ, Alpert NM. Dopamine release during human emotional processing. Neuroimage 2009; 47(4): 2041-5.

[34] Badgaiyan RD, Fischman AJ, Alpert NM. Striatal Dopamine Release During a Cued-Recall Task. Journal of Nuclear Medicine 2006; 47(supp 1): 138.

[35] Narendran R, Frankle W, Mason N, *et al*. Positron emission tomography imaging of amphetamine-induced dopamine release in the human cortex: a comparative evaluation of the high affinity dopamine D2/3 radiotracers [11C]FLB 457 and [11C]fallypride. Synapse 2009; 63(6): 447-61.

[36] Mukherjee J, Yang ZY, Das MK, Brown T. Fluorinated benzamide neuroleptics--III. Development of (S)-N-[(1-allyl- 2-pyrrolidinyl) methyl]-5-(3-[18F] fluoropropyl)-2, 3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer. Nucl Med Biol 1995; 22(3): 283-96.

[37] Farde L, Hall H, Ehrin E, Sedvall G. Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. Science 1986; 231(4735): 258-61.

[38] Christian B, Lehrer D, Shi B, *et al*. Measuring dopamine neuromodulation in the thalamus: using [F-18]fallypride PET to study dopamine release during a spatial attention task. Neuroimage 2006; 31(1): 139-52.

[39] Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci 1998; 18(1): 411-8.

[40] Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 2002; 16(2): 331-48.

[41] Richardson M, Strange B, Dolan R. Encoding of emotional memories depends on amygdala and hippocampus and their interactions. Nat Neurosci 2004; 7(3): 278-85.

[42] Shin LM, Wright CI, Cannistraro PA, *et al*. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry 2005; 62(3): 273-81.

[43] Strange B, Dolan R. Anterior medial temporal lobe in human cognition: memory for fear and the unexpected. Cognit Neuropsychiatry 2006; 11(3): 198-218.

[44] Park J, Gu B, Kang D, *et al*. Integration of cross-modal emotional information in the human brain: An fMRI study. Cortex 2010 Feb; 46(2): 161-9.

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