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Imaging dopamine neurotransmission in live human brain

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Abstract

Dopamine is an important regulator of cognition and behavior, but its precise influence on human brain processing remains unclear because of the lack of a reliable technique to study dopamine in the live human brain. In the recent years, a number of techniques have been developed to detect, map, and measure dopamine released during task performance. Most of these techniques are based on molecular imaging methods and have varying degrees of sensitivity. We developed a single-scan dynamic molecular imaging technique for the detection of dopamine released during task performance in the live human brain. This technique is extremely sensitive and has test–retest reliability. Using this technique, we detected dopamine released during the processing of a number of cognitive, behavioral, and emotional tasks. Since this technique acquires data that cannot be obtained using any other techniques, it extends the scope of neuroimaging research.

Keywords

dopamine; molecular imaging; raclopride; fallypride; cognition; behavior; emotion; attention-deficit hyperactivity disorder

It has long been established that neurotransmitters are important regulators of cognition and behavior. However, very little is known about their influences on human brain processing, due to the lack of a reliable method to study neurotransmission in the live human brain (Badgaiyan, 2011a). Neuroimaging methods commonly used to study human brain and behavior have extremely limited ability to detect task-related changes in neurochemical milieu of the brain. Thus, functional magnetic resonance imaging (fMRI), event-related potential (ERP), magnetoencephalography (MEG), and other imaging tools do not reliably detect task-induced neurochemical changes, even though these tools have made significant contribution to our understanding of human brain and behavior by localizing areas involved in the processing and in establishing temporal sequence of activation.

Because of paucity of data on human neurotransmission, most of the information has been acquired in laboratory animals. But animal data have limited ability to explain higher mental functions of the human brain because those functions either do not exist or are underdeveloped in animals. For most of these functions like abstract thinking, conscious experiences, and decision-making, there is no acceptable animal model and for others models do not reflect the processing in human brain. This includes models of depression and

anxiety. Even for the functions for which validated models are available, it is not clear whether those functions are processed in the same way in the human and animal brains. We know that at least some of these functions are processed differently in the human and animal brains. For example, well-validated animal models exist for reward function. Using these models, dopaminergic influence on reward processing has been studied in great details (Schultz, 2010). These studies have primarily implicated the ventral striatal structures but almost all of the studies on the human reward processing have reported evidence of dopamine release in the dorsal striatum, with or without ventral striatal activation (Pappata et al., 2002). Thus, even after meticulous investigation in animals, reward processing of the human brain remains unclear. It is not difficult to understand why. In animal studies, reward is studied using food or water rewards, which are part of the primary motivation system. In humans, most reward experiments were conducted using a secondary reward like monetary rewards. Therefore, at least the way we have studied the reward system, there is a difference in what is considered a reward by animals and humans. Additionally, cognitive and behavioral functions are significantly influenced by social, ethical, and cultural values in human, but in animals, the effect of these variables is unclear. Even if these factors influence processing in animals, it would be inconceivable to think that their effects on cognition and behavior would be similar to those in humans because animals and humans have different social, ethical, and cultural values. Thus, data acquired in laboratory animals do not necessarily explain the role of neurotransmitters in the processing of human cognition and behavior. The accuracy of their roles could be ensured only if the data are acquired in human brain.

Because of its importance, a number of attempts have been made to detect neurotransmission in the live human brain. In most of these attempts, either MRI (Ashwal et al., 2006) or positron emission tomography (PET) was used (Pappata et al., 2002; Koeppe et al., 1998). Since MRI-based techniques are relatively less sensitive, they are not suitable for detection of small amounts of neurotransmitters released during brain processing. A sensitive MRI technique developed recently is promising, but at this time, it cannot be used in the live human brain because it requires direct injection of probes containing mutated protein directly into the brain tissue (Shapiro et al., 2010).

Most investigators have used PET-based techniques for the detection of task-induced changes in neurotransmission because of their higher sensitivity of detection. These techniques use molecular imaging methods in which competition between endogenously released neurotransmitter and its ligand is exploited. Both the ligand and the neurotransmitter bind to the same receptors and compete with each other for occupancy. Thus, if a ligand is injected into the vein of a volunteer, it binds to the receptors in the brain that have remained unoccupied by the neurotransmitter. The ligand however is displaced from receptors sites if the neurotransmitter is released endogenously. The ligand concentration can therefore be used as a marker for the detection of neurotransmitter release. The concentration of ligand can be measured in different brain areas by radiolabeling it prior to the injection. Radiolabeled ligand can be detected and its concentration measured using the PET.

1 MOLECULAR IMAGING TECHNIQUES

In molecular imaging approach, a volunteer is positioned in a PET camera and a radiolabeled ligand is administered intravenously. After the injection PET, data are acquired every few seconds while the volunteer either lies still or performs a task in the scanner. If the neurotransmitter is released during the scan, the ligand concentration in the receptors decreases because of its displacement by endogenously released neurotransmitter. The brain areas where ligand concentration is altered are localized by comparing the values obtained either at rest or during performance of a control task. The comparison allows detection, mapping, and measurement of the neurotransmitter released during task performance. For the sake of accuracy, instead of ligand concentration, most experiments use values of a number of receptor kinetic parameters as markers for detection of neurotransmitter release. These parameter values are dependent on the rate and amount of ligand displaced from receptor sites. An important parameter value is the binding potential (BP) of ligand. It refers to the number of receptors available to the ligand for binding. Since ligands are assumed to bind only to unbound receptors, the ligand BP and neurotransmitter concentration have inverse relationship. Additional neurotransmitter released by the task into the synaptic space occupies a larger number of postsynaptic receptors thereby reducing the number of receptors available to ligand to bind. Conversely, increased ligand BP indicates reduction in endogenously released neurotransmitter. The use of the values of receptor kinetic parameters also helps to quantify the amount of neurotransmitter release. It however requires prior knowledge of the relationship between the amount of neurotransmitter release and changes in parameter values. All molecular imaging techniques developed to detect task-induced neurotransmission use this basic principle.

Accuracy and sensitivity of detection in this technique depend on a number of factors. The most important being the nature of ligand used. Sensitivity increases with increasing specificity of the ligand. Thus, if a ligand binds only to a specific receptor population, results are likely to be more accurate. However, most ligands bind to a number of receptors at varying proportion, and in addition to receptors, they also bind to the plasma and tissue proteins. Binding of the ligand outside specific receptor population (nonspecific binding) adds to the noise and reduces sensitivity. Another factor in these experiments concerns the amount of ligand binding. For detection of binding and displacement, it is necessary for the ligand to bind in adequate amount. Selection of ligand therefore is an important and challenging step in these experiments. Fortunately, a number of ligands for dopamine receptors have relatively high specificity and have acceptable levels of nonspecific binding. Neurotransmitter studies therefore have primarily been conducted on dopamine neurotransmission. Dopamine ligands however have variable affinity for receptors, and depending on the affinity, these ligands can be detected in different brain areas. Thus, the ligand raclopride, which has relatively low affinity, binds in detectable quantity only in the areas where the density of dopamine receptors is high. These areas include the striatum. Thus, if this ligand is used in a study, dopamine can be detected only in the striatum. The high-affinity dopamine receptor ligands like fallypride and FLB457 on the other hand bind in detectable quantities in a number of brain areas that have low receptor density. These ligands are used for the detection of dopamine outside the striatum (Badgaiyan et al., 2009).

2 BASIC PRINCIPLES AND RECEPTOR KINETIC MODELS

After a ligand is identified and selected, the next challenge involves the measurement of values of receptor kinetic parameters. To accurately detect changes in neurotransmission and to ensure that changes are not due to noise associated with detection or data analysis, values of a number of receptor kinetic parameters are estimated. Estimation of these values is challenging because it requires separation of specific binding (to receptors) from nonspecific binding (outside receptors). This separation is necessary because the PET data acquired during the scan represent the total ligand concentration (specific and nonspecific binding), but for detection of dopamine release, it is necessary to estimate changes in the ligand bound only to dopamine receptors (specific binding). The separation is accomplished using receptor kinetic models. These models are based on Michaelis-Menten equation (Michaelis and Menten, 1913), which was developed about a hundred years ago to describe enzyme kinetics. This equation, with little or no modification, can also be used to describe the rate at which a ligand enters and leaves different spaces in the brain (Badgaiyan, 2011a). These spaces are called compartments and for the sake of simplicity, most kinetic models assume that the ligand travels through three compartments: the plasma compartment, which refers to the ligand in the blood; the nondisplaceable compartment, which includes all substrates to which a ligand binds outside receptors; and the receptor compartment, which refers to the ligand bound to specific receptors (Fig. 1). Thus, using Michaelis-Menten equation, ligand bound to the receptors (specific binding) can be separated and quantified from those bound outside in nondisplaceable compartment (nonspecific binding). This however requires measurement of the value of ligand concentration in plasma compartment. This value is estimated by measuring ligand concentration in the arterial plasma. Using this input, the concentration of ligand in all three compartments can be computed using Michaelis-Menten equation.

The requirement of collecting arterial blood samples at multiple time points during the scan makes this method difficult and impractical in many centers because of highly invasive nature of the procedure. Most studies therefore use the simplified reference region model (SRRM) to estimate specific binding (Gunn et al., 1997; Lammertsma and Hume, 1996). This model does not use arterial plasma concentration as input function. It uses the ligand concentration in a reference region of the brain to estimate nonspecific binding. The reference region in this method is an area where dopamine receptor density is zero or close to zero. The cerebellum is used as reference region by many investigators because of the paucity of dopaminergic receptors in this structure. Due to the absence of receptors, specific binding is close to zero in the cerebellum. The ligand concentration in the reference region therefore equals nonspecific binding or binding in the nondisplaceable compartment. By subtracting this value from the total binding estimated by the PET data in a brain area, values of the specific binding can be estimated. This estimation however assumes uniformity of nonspecific binding in the brain. Even though it is difficult to believe that nonspecific binding is uniform in all brain areas, there is no reason to believe significant variation either. Even though the estimates using SRRM are based on a number of assumptions, the values estimated using this model do not differ significantly from the values measured using arterial input function (Lammertsma and Hume, 1996).

Thus, SRRM allows estimation of the amount of ligand bound to receptors, without the need to draw arterial blood samples. Based on the amount of ligand binding, the model computes the values of a number of receptor kinetic parameters including the ligand BP. These values help us understand the nature of dynamic changes in ligand-receptor interaction. Based on these changes endogenously released neurotransmitter is detected, mapped and measured. Critical receptor kinetic parameters include the rate at which the ligand enters and exits different compartments. The entry and exit from the compartments are denoted by K_1 , k_2 (entry and exit between plasma and nondisplaceable compartments), k_3 , and k_4 (entry and exits between nondisplaceable and receptor compartments) as shown in Fig. 1. At equilibrium, the rate at which the ligand exits a compartment is the same as the rate at which it enters. Thus, K_1 equals k_2 and k_3 equals k_4 . Eventually, K_1 equals k_4 .

To examine the ability of SRRM to detect task-induced release of dopamine, the BP of a dopamine receptor ligand ^{11}C -raclopride was measured at rest and during task performance in recent experiments (Koepp et al., 1998). In this experiment, task-induced changes in the ligand BP was detected by scanning volunteers at rest and again while they played a video game. The ligand BP was estimated in the two scans separately and compared. The comparison revealed the striatal areas where BP was reduced during task performance. As discussed earlier, the reduction indicated dopamine release. Even though dopamine released during task performance was detected in this experiment, this method did not get wide acceptance because of the lack of sensitivity. The task used in this experiment (playing video game) has a number of cognitive and behavioral components (e.g., motor planning and movement, reward, learning, memory, behavioral reinforcement, attention, sensory motor integration, and visual and auditory processing), and most of these components are processed using dopaminergic neurotransmission. The task therefore is likely to release a large quantity of dopamine. But during processing of an isolated cognitive and behavioral function, the amount of dopamine release is very small in comparison with the task of playing video game. This method is not likely to reveal changes associated with isolated cognitive or behavioral processing primarily because of the need to compare data acquired in two separate scan sessions separated by several days or weeks. The method requires acquisition of control BP values at rest in one scan and values during task performance in a second scan. Since dopamine is involved in the processing of a number of brain functions, the baseline dopaminergic activity during the two sessions is likely to be different. In the two-scan method, this difference cannot be accounted for. It reduces sensitivity of detection. This method therefore cannot reliably detect small amounts of dopamine released during an isolated brain processing (Badgaiyan, 2011a; Pappata et al., 2002; Fischman and Badgaiyan, 2006).

To detect dopamine released during processing of a single cognitive or behavioral function, it is important to develop a technique that is sensitive and is able to detect the release of a very small quantity of dopamine. This would require acquisition of the control and task-induced values of BP in the same scan session. Analysis of the data acquired in a scan session that has two different task conditions is technically challenging because SRRM assumes that physiological steady state is maintained during the entire scan session. A change in task condition violates this assumption, and therefore, SRRM cannot be used to estimate the values of BP and other receptor kinetic parameters. To circumvent the

requirement of steady state, investigators have used a variety of approaches. The initial approach involved comparison of the values of receptor kinetic parameters measured during task performance with a “normalized” map of the values generated using data previously acquired in a “control” experiment (Pappata et al., 2002). This approach however is not significantly different from the two-scan method because both require comparison of data acquired in two separate scan sessions.

A better approach was used in the extended simplified reference tissue model, the E-SRTM (Zhou et al., 2006). In this model, data are acquired during a control condition first and then under the task condition in the same scan session. Data acquired during the scan are then split in two datasets: before and after an intervention or during performance of the control task, and during performance of the study task. Each dataset is then either extrapolated (control dataset) or intrapolated (study dataset) to make two complete sets of data. Each set represents data acquired under physiological steady state (either control or study task). This approach allows the use of SRRM for estimation of receptor kinetic parameters separately during the control and study task. By comparing parameter values estimated under the two conditions, dopamine released during task performance can be detected, mapped, and measured. The extrapolation and intrapolation of datasets in this method use a number of assumptions concerning ligand-receptor interaction. These assumptions limit the accuracy of detection.

3 SINGLE-SCAN DYNAMIC MOLECULAR IMAGING TECHNIQUE

Our laboratory adopted a different approach (Alpert et al., 2003). We modified the SRRM to allow changes in physiological state during the scan session. The modified model, called the linear extension of simplified reference region model (LE-SRRM), allows the estimation of the values of receptor kinetic parameters at different time points during the scan. Based on these values, the rate at which ligand dissociates from receptors is estimated. Since additional dopamine released during task performance displaces additional ligand from receptor sites (increasing the rate of displacement), the rate of ligand displacement is a good marker for endogenous dopamine release. This method therefore allows precise detection, mapping, and measurement of dopamine released during task performance.

Using this model, we developed a single-scan dynamic molecular imaging technique (Alpert et al., 2003; Badgaiyan et al., 2003). In this technique, after volunteers have received an intravenous bolus of a radiolabeled ligand, they are asked to perform a task in the PET camera. The PET data are acquired every 30–60 s immediately after the ligand injection. Based on these data, time-dependent changes in the ligand concentration and values of receptor kinetic parameters are estimated using the following operational differential equation:

$$PET(t) = R \cdot C_R(t) + K_2 \cdot \int_0^t C_R(u) du - k_{2a} \int_0^t PET(u) du - \gamma \int_0^t \nu(u-T) e^{-n(u-T)} PET(u) du$$

where C_R is the radioligand concentration in the reference region, PET is the concentration in an “activated” 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, k_{2a} includes information about dissociation from the receptor, γ represents change in the rate of ligand displacement, t denotes the measurement time, T is the task initiation time, and $v(u - T)$ is the unit step function.

Values of the receptor kinetic parameters are estimated at each voxel at each time point (blocks of 30–60 s) during performance of the control and study tasks. The values acquired during the two task conditions are compared, and based on this comparison, changes in the values are computed and mapped. Based on these changes, dopamine released during task performance is detected and mapped (Alpert et al., 2003).

As mentioned earlier, E-SRTM allows measurement of the ligand BP and other receptor kinetic parameters during a specific time frame within the scan (Zhou et al., 2006). Thus, E-SRTM and LE-SRRM use different approaches to detect dopamine. In LE-SRRM, it is detected by measuring changes in the rate of ligand displacement during task performance (γ), while in E-SRTM, detection is based on the ligand BP measured before and after an intervention. The SRRM's assumption of steady state during the experiment is violated in both models. The two models use different strategies to eliminate the assumption of steady state. LE-SRRM allows dissociation rate of ligand to change in response to an altered synaptic level of neurotransmitter; therefore, it does not assume maintenance of a steady state. The E-SRTM reconciles the violation of steady state by assuming that the data acquired before and after the intervention are separate datasets. Since the two models use different approaches and parameters to detect dopamine release, analysis of the PET data using both models increases the reliability of detection.

4 USE OF MULTIPLE KINETIC MODELS

We have found significant agreement in detection and mapping estimated by the two models (LE-SRRM and E-SRTM). However, when both models are used to analyze a dataset, the output is reconciled using predefined criteria (Badgaiyan and Wack, 2011a). In our laboratory, a blob (>5 contiguous voxels) is considered “activated” only if all of the following conditions are met: (a) there is a significant change ($p < 0.05$) in the values of the rate of ligand displacement (γ) estimated using LE-SRRM after task initiation; (b) the ligand BP (measured using E-SRTM) is significantly lower ($p < 0.05$) during performance of the study task than that during the control task; (c) there is a significant increase in dissociation coefficient (k_{2a}) measured using E-SRTM during study task performance; and (d) maxima of blobs identified as “activated” by LE-SRRM and E-SRTM are located within 6 mm of each other to account for Gaussian smoothing involved in the processing. By using these criteria, we have been able to obtain results that have excellent test–retest reliability (Badgaiyan and Wack, 2011b).

The single-scan dynamic molecular imaging method is extremely sensitive in the detection of dopamine if right ligand is used in the experiment. As discussed earlier in the text, low-affinity ligands like raclopride bind and displace in detectable quantity only in the striatum; these agents are therefore ideal to study striatal dopamine. To study dopamine outside the striatum, high-affinity ligands like fallypride (Badgaiyan et al., 2009) and FLB457 (Farde et

al., 1997) are used. In our laboratory, raclopride (labeled with ^{11}C) was used to detect and map dopamine released in the striatum during performance of a number of cognitive and behavioral tasks (Badgaiyan, 2010, 2011a; Fischman and Badgaiyan, 2006; Badgaiyan et al., 2003, 2006, 2007, 2008a; Badgaiyan and Wack, 2011a). We have also used the highaffinity ligand fallypride (labeled with ^{18}F) for the detection of dopamine outside the striatum (Badgaiyan et al., 2009). We have found ^{18}F -fallypride to be a very sensitive ligand for the detection of dopamine outside the striatum, but due to long binding time (Mukherjee et al., 2002), its displacement from striatal receptors is difficult to detect. We used ^{18}F -fallypride to detect dopamine released outside the striatum during emotional processing (Badgaiyan et al., 2009). In this study, we were able to detect the release of dopamine in a brain area as small as the amygdala. We also observed dopamine release in the medial temporal lobe and prefrontal cortex (Fig. 2A and B). Since these areas are most frequently associated with emotional processing, the data indicated that the detection using ^{18}F -fallypride is reliable and sensitive.

Because of its reliability, single-scan dynamic molecular imaging technique developed in our laboratory has been used by a number of investigators to study dopamine release in the human brain during performance of a number of cognitive and behavioral tasks (Badgaiyan et al., 2003, 2007, 2008a,b, 2009; Badgaiyan and Wack, 2011b; Badgaiyan, 2010; Badgaiyan and Fischman, Under Review; Backman et al., 2011; Christian et al., 2006). In the studies conducted in our laboratory, we have identified precise location of dopaminergic neurons involved in the processing of a number of memory, attention, and emotional tasks. These tasks include motor planning, implicit and explicit motor memory, nonmotor explicit and implicit memory, executive inhibition, and spatial attention tasks.

5 STUDY OF PATHOPHYSIOLOGY OF PSYCHIATRIC CONDITIONS

Since the single-scan dynamic molecular imaging technique provides information that cannot be obtained by other techniques, it is a valuable tool to examine the validity of hypotheses concerning pathophysiology of psychiatric and neuropsychiatric conditions. We are currently examining these hypotheses to understand the nature of dysregulated dopamine neurotransmission in psychiatric conditions. Valuable information concerning dopamine neurotransmission in these conditions was obtained in these experiments. In a recent experiment, we studied an important hypothesis concerning dopaminergic activity in attention-deficit hyperactive disorder (ADHD). Dysregulation of dopamine neurotransmission in ADHD is suggested by a number of pharmacological and experimental studies (Genro et al., 2010), but the nature of dysregulation remains unclear because data acquired using indirect methods suggested either increased or decreased activity of dopamine in these patients. Evidence that suggests hypoactivity includes small volume of the basal ganglia (Aylward et al., 1996; Castellanos et al., 1994) and reduced striatal blood flow (Lou et al., 1989). The hypoactivity concept, however, is not consistent with the observation that many dopamine agonists have no therapeutic effect. Thus, L-dopa or the combination L-dopa-carbidopa does not improve any of the laboratory parameters of either motor activity or attention in ADHD patients (Langer et al., 1982). Therefore, many investigators have suggested that dopamine is hyperactive in ADHD particularly because increased dopaminergic activity disrupts the executive and reward systems leading to motor

hyperactivity and attenuation of inhibitory control (Viggiano et al., 2002; Oades, 2002). Studies on animal models of ADHD did not resolve the controversy because different models showed evidence of either hyperactive or hypoactive dopaminergic activity (Miller et al., 2012; Russell, 2002).

We proposed that the contradictory findings could be due to the inability of indirect methods to differentiate dopamine activity at rest from the activity during brain processing. While continuous release of dopamine at rest (tonic release) maintains dopaminergic tone, additional dopamine released during processing of dopamine-dependent tasks (phasic release) is responsible for carrying out functions that are mediated by dopamine. The tonic release and phasic release are interdependent to some extent (Grace, 1991). If the tonic release is depressed and there are fewer “occupied” dopamine receptors, higher amount of phasic dopamine is required to perform a task. Conversely, if the tonic release is at above normal level, smaller amount of phasic dopamine is required to perform the same task.

We hypothesized that in ADHD, tonic release of dopamine is depressed and there is compensatory increase in the phasic release. If this were the case, earlier studies that have indirectly measured the tonic pool were expected to find reduced dopaminergic activity and the studies that have indirectly measured the phasic release could find enhanced activity. The conventional indirect methods of estimating dopaminergic activity (e.g., measurement of levels of dopamine metabolites in serum, urine, or CSF and estimation of receptor density) do not differentiate activity due to tonic or phasic release and therefore could arrive at contradictory conclusions based on indirect detection of either tonic or phasic release.

Our hypothesis of reduced tonic and increased phasic release of dopamine in ADHD patients cannot be validated using conventional methods of neuroimaging because it would require direct measurement of the tonic and phasic release separately. We therefore used the single-scan dynamic molecular imaging to measure tonic and phasic release. The tonic release was estimated by measuring dopamine release at rest, and to measure the phasic release, volunteers were asked to perform Eriksen’s flanker task (Eriksen and Eriksen, 1974), which requires volunteers to make quick response to a target stimulus while suppressing unwanted responses suggested by irrelevant stimuli. As expected, patients with ADHD perform poorly in this task because of their reduced ability to suppress unwanted responses. We compared the tonic and phasic release of dopamine in ADHD patients and matched healthy volunteers. The comparison revealed that the tonic release in the patients is significantly lower than that in healthy control volunteers and that the phasic release was considerably higher. In healthy volunteers, dopamine was released phasically in the head of the left caudate and in the putamen bilaterally (Figs. 3 and 4), but in patients, it was released in both, the right and the left caudate in addition to the putamen. These findings validated our hypothesis of reduced tonic and increased phasic release. It provided a novel insight into the neuropathology of ADHD.

These findings suggest that the primary deficit in ADHD is reduced tonic release of dopamine. It however appears that the clinical symptoms are due to compensatory enhancement of the phasic release. Evidence suggests that the processing of central executive processing is dependent on dopamine neurotransmission and it is impaired at high

levels of dopamine (Roesch-Ely et al., 2005; Robbins and Arnsten, 2009; Vijayraghavan et al., 2007). Since the primary deficit in ADHD is reduced tonic release, it can be treated by agents that raise the tonic pool. These agents include blockers of dopamine transporter (DAT) such as methylphenidate (Biederman et al., 2005). By inhibiting reuptake into presynaptic neurons, DAT blockers effectively increase the tonic pool (Volkow and Swanson, 2003). By increasing the tonic pool, these drugs correct the initial deficit preventing compensatory enhancement of the phasic release, thereby reducing clinical symptoms. Thus, the single-scan dynamic molecular imaging technique can help in understanding the pathophysiology of psychiatric and neuropsychiatric conditions that are associated with dysregulated neurotransmission.

In the past few years, the single-scan dynamic molecular imaging technique has been used by us and others (Badgaiyan et al., 2003, 2007, 2008a,b, 2009; Badgaiyan and Wack, 2011b; Badgaiyan, 2010; Badgaiyan and Fischman, Under Review; Backman et al., 2011; Christian et al., 2006) to reliably detect and map dopamine released during performance of a number of cognitive, behavioral, and emotional tasks in healthy volunteers (Badgaiyan et al., 2003, 2007, 2008a, 2009; Badgaiyan and Wack, 2011b; Badgaiyan, 2010) and psychiatric patients (Badgaiyan and Fischman, Under Review; Badgaiyan et al., 2008b). Data obtained in these experiments helped us precisely define and confirm the role of dopamine in human cognitive and behavioral processing. Thus, by demonstrating dopamine's involvement in the central inhibitory function, we confirmed a fact that has long been suspected (Casey et al., 2000). Additionally, by localizing clusters of striatal neurons involved and by following their cortical connections, the data helped us understand how striatal and frontal areas interact to provide effective inhibition. It was interesting to observe that in healthy volunteers, we observed dopamine release during inhibition in the medial aspect of the head of caudate only on the left hemisphere and this area receives input from the orbitofrontal cortex also only on the left side (Ferry et al., 2000). It underscores lateralized processing of inhibitory functions in the human brain.

Since information concerning neurochemical changes associated with the brain processing cannot be obtained in the live human brain using any other method, the single-scan dynamic molecular imaging technique expands the scope of neuroimaging research by providing an additional tool, which allows detection, mapping, and measurement of an additional parameter (neurochemistry) of cognitive and behavioral control. The technique therefore has immense potential to help us understand human brain and its control processes.

6 LIMITATIONS AND FUTURE DIRECTIONS

Currently, the technique is at early stages of development. Therefore, it has a number of limitations. The most important limitation is its limited scope. At this time, it can be used to detect only dopamine neurotransmission. Suitable ligands for detection of other neurotransmitters and neuromodulators have not yet been identified and tested. If other neurochemicals released during brain processing cannot be detected, it will be difficult to formulate a comprehensive model of human cognitive and behavioral control. Another issue concerns simultaneous detection of multiple neurotransmitters. Since the single-scan dynamic molecular imaging technique cannot simultaneously detect multiple ligands

because PET detectors do not have ability to differentiate positrons released from different compounds, it does not mean that the technique cannot be modified to allow simultaneous detection of multiple ligands. It would require the development of a receptor kinetic model and modified parameters for PET data acquisition (Badgaiyan, 2011a,b). Another limitation concerns its inability to estimate temporal sequence of activation. Currently, it can localize the activated brain areas but cannot determine the sequence of activation if dopamine is released in multiple areas during task performance. This information is critical to understand neural network involved in the processing. Again, at least theoretically, temporal information could be obtained by appropriately spacing the data acquisition and task protocols (Badgaiyan, 2011a,b). Another issue that needs attention is the integration of data acquired using single-scan dynamic molecular imaging technique with the data obtained using other neuroimaging methods particularly fMRI, ERP, and MEG. To accomplish this, algorithms that allow coregistration of images and functional data obtained using different techniques need to be developed. Since different neuroimaging techniques acquire data on different aspects of brain processing, coregistration of functional data will provide a comprehensive picture and allow the development of an objective data-based neural models of human cognitive and behavioral processing.

7 SUMMARY

The single-scan dynamic molecular imaging is an evolving technique, which extends the scope of human neuroimaging research by allowing the study of neurochemical change associated with the brain processing. It exploits the competition between endogenous neurotransmitter and its ligand for receptor binding. In this technique, after volunteers are positioned in the PET camera, they receive an intravenous bolus of a radiolabeled dopamine receptor ligand (either ^{11}C -raclopride or ^{18}F -fallypride). Immediately after the injection, PET data are acquired dynamically at 30–60 s intervals and volunteers are asked to perform a task in the scanner. The PET data are analyzed using receptor kinetic models developed to detect, map, and measure dopamine released during task performance. We have used this technique to study a number of cognitive and behavioral functions and to examine hypothesis concerning the pathophysiology of psychiatric and neuropsychiatric conditions. The single-scan dynamic molecular imaging technique allows acquisition of data that cannot be reliably obtained using any other method.

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FIGURE 1.

A schematic diagram of the three-compartment model.

FIGURE 2.

Emotional processing in healthy volunteers: dopamine was released in the amygdala (A) and medial temporal lobe (B) during emotional processing. The figures show t-maps of the rate of ligand (^{18}F -fallypride) displacement before and after task initiation. Maps are superimposed on mean PET images and represent changes across volunteers. The time–activity curve shows the concentration history (circles) and least square fits (solid line) for the ligand in the activated regions. There was a significant increase in the rate of ligand displacement after task was initiated (vertical line). The ligand concentration is expressed as kBq/cm^2 .

FIGURE 3.

Response inhibition in healthy volunteers: The striatal areas where the rate of ligand displacement increased significantly during inhibition of unwanted responses (in the incongruent condition of Eriksen's flanker task) are shown on the t-map. The most significant increase was observed on the dorsal aspect of the body of the left caudate. The time–activity curves show the ligand concentration (open circles) and least square fit (solid lines) in a striatal area (upper curve) and in the reference region (lower curves). The data on the left of the vertical lines were acquired during the control task (congruent condition) and those on the right were obtained during response inhibition (incongruent condition). Significant reduction in ligand concentration after initiation of the inhibition task (incongruent condition) suggests increased rate of ligand displacement during task performance. The increase was due to competitive displacement induced by endogenous dopamine release. There was no significant change in the rate of ligand displacement in the reference region (cerebellum). This analysis used the linear extension of reference region tissue model (LE-SRRM).

FIGURE 4.

Response inhibition in healthy volunteers: The t-maps generated using extended simplified reference tissue model (E-SRTM) show striatal areas where the ligand binding potential decreased significantly during inhibition of unwanted responses (incongruent condition of Eriksen's flanker task) in comparison with the control condition (congruent condition of the Eriksen's flanker task). It was most significant in the left caudate and putamen. These areas are located in close proximity to the areas where increased rate of ligand displacement was observed in the experiment (Fig. 3). An agreement in the data computed using two different receptor kinetic models significantly enhances the reliability of detection.