Assessing Dopaminergic Neurotransmission with PET: Basic Theory and Applications in Alcohol Research

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Abstract: Over the last two decades, using PET imaging to assess changes in endogenous dopamine has become a standard neurochemical research technique. Initially, investigators focused on the *in vivo* study of direct pharmacological manipulation of the dopamine system (e.g., amphetamine, cocaine, methylphenidate). More recently, there has been a shift toward studying the role that dopamine plays in cognitive processes and in response to commonly used drugs with subtler effects on the dopamine system. Here, we outline the conceptual foundations of using PET to assess alterations in brain dopamine, and provide the reader with important theoretical constructs that must be addressed when designing such studies. Data from recent work with dopaminergic PET ligands are used to provide concrete examples of relevant design considerations.

Keywords: Position emission tomography, neurotransmitter, dopamine D2 receptor, dopamine release, tracer kinetic modeling.

WHY WE CAN USE PET TO "SEE" NEUROTRANSMISSION

Many neuroligand PET tracers are compounds that bind reversibly to a neuronal protein, such as a receptor or a transporter. The most commonly used quantitative endpoint is "binding potential" (BP), which has a general operational definition of B_{avail}/K_D. B_{avail} is the concentration of receptors available for binding, and K_D is the apparent affinity constant of the radioligand for its target (also, see Fig. **1**). (Note: there are three variants of BP that differ slightly, the subtle mathematical distinctions between which are beyond the scope of this paper. The reader is referred to Innis *et al.*, 2007 [1], for a thorough explication of the various derivations of BP. A typical interpretation of BP is that it represents receptor or transporter density, or "number of receptors". Although this is a reasonable interpretation, the very definition of B_{avail} – receptors *available* for binding - accounts for the influence of endogenous neurotransmitter (NT), and lays the foundation for using PET to index changes in neurotransmission. The concept is simple: if a radiotracer is sensitive to changes in endogenous neurotransmitter via competitive binding at the target, that ligand is a candidate for giving us a window into neurotransmission of the human brain.

The most-often used paradigm for assessing changes in NT levels involves two PET scans, each with a single bolus injection of tracer (although single-session designs exist; see [2-4]). One session serves as the "resting" or "baseline" scan; the "challenge" scan is intended to perturb the neurotransmitter of interest, with a pharmacological, cognitive, or motor task. Differences in BP between the baseline and challenge scan are believed to be the result of changes in endogenous NT. For example, if the challenge provokes an increase in endogenous NT (e.g., a surge in dopamine after amphetamine administration), then the NT will occupy a greater proportion of receptors relative to baseline. The measured PET signal will therefore reflect an apparently lower B_{avail} compared to the "baseline" state. As described below, this technique requires several assumptions that may or may not be met, depending upon experimental design.

A WORD ON DOPAMINE

The principles outlined in this paper are, in theory, applicable to any classical neurotransmitter or neuropeptide system. However, the majority of the literature on measuring neurotransmission with PET revolves around dopamine (for extensive review, please see [5, 6]), as will the examples cited in this paper. It should be noted that researchers at the University of Michigan have been successful at quantitating changes in endogenous opioids [7-10]. However, published attempts at demonstrating measureable increases in serotonin levels with radioligand PET have been unsuccessful [11-13], although a recently introduced 5-HT_{1B} compound shows promise [14]. As outlined below, individual ligand characteristics indeed play a part in the detectability of changes in dopamine. But the dominance of dopamine within the neuroPET literature is likely the combination of three factors: [1] the now-classic demonstration that the DA D_2/D_3 antagonist raclopride (which is amenable to labeling with the posi-

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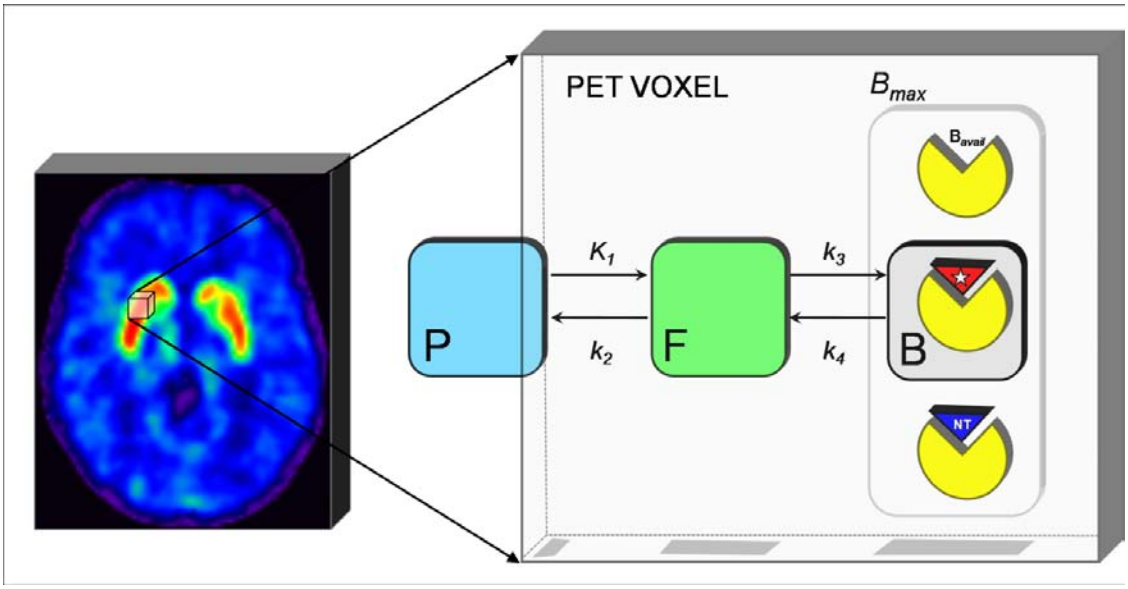

Fig. (1). Fundamental components of the two-tissue compartment (2T) tracer kinetic model. Tracer kinetic modeling allows us to take data from PET images, such as the [^{11}C]raclopride scan shown on the left, and estimate receptor availability for a given radioligand. The diagrammatic representation of a PET voxel (right) contains the basic elements of the 2T model. More complex modeling schemes exist, but we have elected to present the 2T model for simplicity. The underlying concept is that the tracer can exist in one of three possible states within the voxel: in plasma (P), or in one of two brain tissue compartments, either "free" (F), or "bound" (B) to a receptor. Mathematically, plasma is not considered a compartment, but is positioned partially within the voxel to illustrate that blood accounts for about 5% of brain tissue volume. Arrows denote the direction of tracer flux between the different states within the voxel. K_1 and k_2 are the rate constants that describe the speed with which tracer is transported between plasma and tissue. The transition from F to B is governed by k_3, which is the product of two terms: the association rate constant (k_{on}) of the tracer for the receptor, and B_{avail}, the number of receptors *available* for binding. The dissociation rate constant of the tracer (k_{off}) is equivalent to k_4, and describes how quickly the tracer moves from B to F. The total number of receptors in the tissue, B_{max}, is comprised of receptors in three states: unbound receptors (B_{avail}), receptors bound by tracer (B; red triangle labeled with white star), and receptors bound by endogenous neurotransmitter (blue triangle, labeled with 'NT'). The equilibrium dissociation constant of the tracer for the receptor, K_D, is defined as k_{off}/k_{on}. In the ideal, the ratio of k_3/k_4 is equivalent to B_{avail}/K_D, which in turn, is referred to as "binding potential" (BP), a commonly used index of receptor availability. In practice, one often estimates an index proportional to BP from imaging data. (B_{max} is typically not estimated). Tracer kinetic theory describes the movement of tracer between states in terms of ordinary differential equations. The solution to these equations, and its comparison to an experimental data set (like that from our hypothetical voxel, observed over time) lead to an estimate of BP. For more detailed treatment of BP, or of parameter estimation in general, the reader is referred to [1, 55], respectively.

tron emitter [^{11}C]) was displaceable by dopamine [15-18]; [2] the massive amount of projections of dopamine neurons that arise from the midbrain and terminate in the striatum, which provided a robust platform for *in vivo* pharmacological studies that convincingly demonstrated PET could be used to detect dopamine release [e.g., 18, 19-21]; and [3] the fact that the nigrostriatal and mesolimbic dopamine systems play key roles in multiple psychiatric and neurologic disorders, including addiction, schizophrenia, bipolar disorder, Tourette's, obsessive-compulsive disorder, and Parkinson's Disease.

BASIC TRACER KINETICS: HOW LIGAND PROPERTIES AFFECT STUDY DESIGN

At a very practical level, the underlying kinetic properties of a tracer are not likely to directly guide an investigator's selection of radioligand. However, it is instructive to understand the basics of tracer kinetic modeling. This brief explication will illustrate the principles that govern tracer behavior, which, in turn, affect experimental design.

Quantitative estimates of BP are achieved through application of tracer kinetic modeling to the PET data. Tracer kinetic modeling describes the behavior of a tracer in terms of "where" the tracer can exist in brain tissues (conceptualized as "compartments") and the rate constants that characterize the movement of tracer between plasma and the various tissue compartments (see Fig. **1** for details). Given an appropriate compartmental model for any given tracer, it is possible to obtain estimates of BP by determining the values of the rate constants that best describe the real PET data. Although these rate constants will vary slightly from person to person, it is generally accepted that tracers behave similarly across individuals, and are the same within a given subject between sessions.

As mentioned above, the term BP contains the K_D, or affinity constant, of the tracer for its target. Although K_D certainly plays a role in the sensitivity of any given compound to competition by the endogenous ligand, attempts to predict displaceability by K_D values have not been successful, despite the number of theories put forth [6, 22]. This seems counter-intuitive, as it is reasonable to assume that how "tightly" a competitive ligand binds will be directly related to how sensitive it would be to competition by the endogenous NT. One explanation for this apparent paradox lies within the "pixel" illustrated in Fig. (**1**). Consider that, if a tracer is displaced by endogenous NT, as the tracer molecule moves from the "Bound" to the "Free" compartment, the radioactivity of this molecule is still being measured within

the pixel- we cannot tell whether a tracer is "bound" or "free", only that its positron emission is being detected. For an overall decrease in PET signal to be measured, the tracer must leave the pixel, return to the plasma, and thus be removed from brain tissue. The rate constant that governs this process is k_2, the movement of tracer from the "Free" compartment back to the plasma. In fact, simulation studies have shown that k_2 predicts how sensitive a given tracer is to displacement by endogenous NT [23]. This observation was in good agreement with the authors' survey of the literature, which documented differential sensitivity of dopaminergic D_2/D_3 tracers to amphethamine-induced dopamine release. Regardless of whether the sensitivity of a tracer to changes in endogenous NT is derived empirically or theoretically, knowledge of how the tracer behaves is crucial for an effective study design.

If the effect of interest is a putative increase in endogenous NT, there are two basic study designs: blocking or displacement. "Blocking" experiments deliver the stimulus prior to tracer injection, raising the concentration of NT and occupation of receptors by NT, and preventing tracer molecules from binding. In a displacement study, the stimulus is delivered after the tracer injection, and relies on the assumptions that [1] the tracer is easily displaced by increases in endogenous NT, and [2] the k_2 value is such that the displacement is measureable. The relative usefulness of both paradigms is discussed below in terms of tracer kinetic principles and practical considerations. To start, we will briefly describe the relative merits of two popular dopaminergic tracers with respect to general study design.

[^{11}C]Raclopride (RAC) is by far the most commonly used tracer for assessment of changes in endogenous striatal dopamine. RAC has nM affinity for D_2/D_3 receptors, is sensitive to both increases and decreases in dopamine concentration, and can be used effectively with both blocking and displacement designs. The major disadvantage of RAC is the relatively poor signal-to-noise properties of the tracer, which prevent investigators from interrogating extrastriatal regions that have low densities of D_2/D_3 receptors, and have poor RAC signal relative to the background signal.

[^{18}F] Fallypride (FAL) is a D_2/D_3 tracer with exceptional affinity (pM), is competitive with endogenous dopamine, and has signal-to-noise properties that allow testing of hypotheses in extrastriatal areas such as thalamus, amygdala, and cortex. However, FAL is not as easily *displaced* by endogenous dopamine as RAC. To obtain measurable changes in FAL signal as a result of increased endogenous DA, it may be better to design an experiment in which the stimulus begins prior to tracer injection and is maintained throughout the experiment, so that sustained increases in dopamine will prevent FAL from binding, and result in a lower BP value relative to a baseline state. Below, we revisit these concepts in the more specific context of experiments involving alcohol and related cognitive processes.

In a single bolus "challenge" experiment, the concentrations of both tracer and (presumably) endogenous NT are changing continuously over time (Fig. **2**). Understanding the interaction of the behavior of the tracer over time (described by our rate constants of interest) with the kinetics of the endogenous ligand is crucial for maximizing detection of increases in NT. Decreases in BP are most detectable when the peak of endogenous NT coincides with the peak of free tracer concentration [23-25]. Thus, if one can predict accurately when the stimulus will have the greatest effect, a "blocking" study would be most likely to produce robust effects of increased dopamine concentration [26, 27], com-

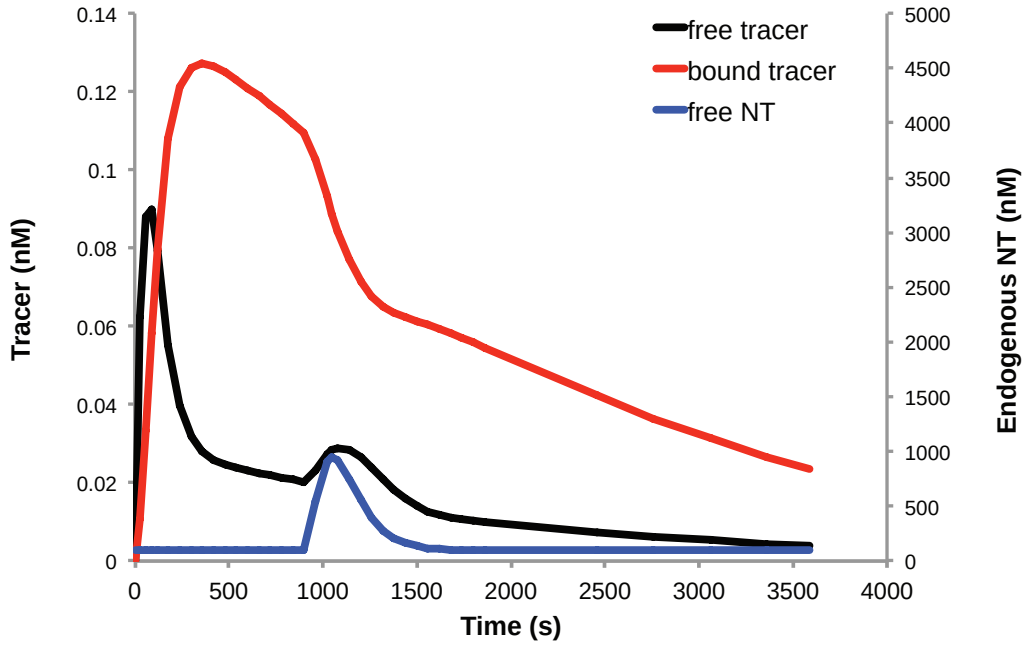

Fig. (2). Tracer behavior changes in the presence of changing neurotransmitter levels. Hypothetical curves of free tracer, bound tracer, and neurotransmitter levels during the course of a PET scan session following a bolus injection of tracer. Data are from noise-free simulations based on raclopride kinetics [23]. As the concentration of a neurotransmitter (NT, blue) increases during a "challenge", the NT displaces the bound tracer (red), and causes a concomitant increase in free tracer (black). As described in the text, understanding how the kinetics of the NT curve interacts with the dynamic behavior of the tracer is vital for good study design.

pared to a "displacement" paradigm. Accurate timing of a stimulus is also important for reduction of inter-subject variability. If identical increases in dopamine occur at different times relative to tracer injection, the result is different BP values for the challenge scans - and different estimates of relative changes in dopamine levels [25]. Slight differences in timing of the stimulus relative to tracer injection may translate into differences in timing of dopamine responses- and thus increase the variability across a sample. Given that it is difficult to have absolute control over timing of tracer synthesis, delivery, and injection (especially with compounds with short half-lives, like [^{11}C]), maintaining consistent timing of a stimulus delivered prior to tracer delivery may prove difficult and may not be advisable. With a compound like FAL, which has a relatively long radionuclide $t_{1/2}$, achieving consistent intervals between stimulus presentation and tracer injection is eminently more feasible.

INFLUENCES OF INTER-INDIVIDUAL DIFFERENCES ON STUDY OUTCOME

Oral ingestion of pharmacological agents is often used to provoke dopamine release. This approach adds an important caveat to study design that is well-illustrated with alcohol challenge studies. Even if the dose, volume, and timing of an orally consumed alcoholic drink are tightly controlled, this will result in different *timing* of alcohol delivery and differential *doses* of alcohol that reach the brain. This is because people vary widely in the absorption, distribution, and elimination of alcohol [28-32]. If oral dosing results in different timing and dose of drug to the brain, then the neurotransmitter response to the drug of interest will be highly variable across subjects. As discussed above, variability in the timing of the dopamine response could easily confound study outcome measures.

Three studies examined alcohol-induced dopamine release with RAC and oral alcohol administration. The first found no effect of oral alcohol on striatal dopamine release; however, this group did not specifically examine the ventral striatum, which is an important structure in reward pathways [33]. Boileau *et al.* [34] and Urban and colleagues [35] each found modest effects of oral alcohol administration on ventral striatal dopamine release. However, the effects in the former study had a high degree of variance [34]; the latter study had a relatively wide range of blood alcohol levels across subjects [35]. Additionally, it is possible that the non-pharmacologic sensory properties of alcohol contributed to the effect they detected [36, 37]. However, it is certainly plausible that oral alcohol administration could have contributed to lack of an effect [33], variation in blood alcohol levels [35], or the variable nature of changes in BP [34].

We elected to study the effects of alcohol on dopamine release without the inherent variability of oral dosing by giving alcohol intravenously with the Alcohol Clamp technique [28, 29]. The Alcohol Clamp uses a physiologically-based pharmacokinetic (PBPK) model to determine the rates of infusion necessary to achieve a pre-specified target breath alcohol (BrAC) level. The PBPK model takes into account an individual's alcohol elimination rate, a parameter estimated from age, gender, height and body weight. With this method, investigators can precisely control the timing of alcohol delivery and greatly minimize inter-individual variation in brain exposure to alcohol – and hence, potential variation in timing and magnitude of dopamine release. Even with the alcohol clamp paradigm, we were unable to detect consistent dopamine responses across healthy social drinkers who received similar subject instruction, and identical timing and dosing of IV alcohol [38]. Similar results were reported recently by another group [39]. This negative finding is supportive of preclinical studies that demonstrate a dissociation between brain ethanol concentration and brain dopamine concentration [36, 37]. It also lends support to our hypothesis that the intra-oral sensory properties of alcohol may play a prominent role in the dopamine release observed with oral alcohol administration paradigms.

WHAT'S IN A BASELINE? (OR, BASELINE, BASELINE, WHEREFORE ART THOU?)

The two-scan paradigm depends on a comparison of BP obtained during a challenge scan to that from a baseline scan. Thus, baseline BP helps dictate the measured magnitude of the effect of a stimulus of interest. In principle, the experimental design assumes that the only manipulation of dopamine is caused by the stimulus of interest during the challenge scan. Meeting this assumption is not as simple as one may assume, given that cognitive states and behavior can have surprisingly strong effects on endogenous dopamine levels [5]. So, what constitutes a proper "baseline"? A condition during which the subject is merely resting quietly, or a scan during which the subject is completing a control task (or given a placebo)? The answer lies in the experimental question, and the confidence of the investigator that dopamine responses are not invoked by the control task. Even subtle things, such as how the investigator sets up subject expectations during the course of a two-scan experiment, can alter "baseline" dopamine levels [40]. Placebo conditions can also increase striatal dopamine [41-43], which could result in underestimation of any bona fide increase in dopamine levels, or overestimation decreases in dopamine. Controlling for small motor movements and/or general attention (like clicking a mouse key to generate a response) during a baseline scan may indeed be advisable. This type of control is particularly appropriate because no two humans will have identical mental activity at "rest". One subject may be thinking of all of their unattended obligations, while another may be ruminating over a fight with a friend. Moreover, if the natural mode of "stimulation" also encompasses other stimuli in addition to the challenge stimulus of interest (e.g., smell, taste, touch, concomitant motor acts), then an ideal baseline would include all extraneous stimuli save for the challenge of interest. However, if that carefully matched "baseline" also incorporates stimuli or cognitive processes that could elicit a potential DA response, then this may complicate interpretation of the result.

Consider an interesting study by Scott *et al.* [4], which examined dopamine release as a consequence of nicotine ingestion (it should be noted that this study utilized a single-scan design; however, there is still the inherent assumption of a "baseline" state during the early part of the scan). The act of smoking delivers nicotine, but this habitual behavior involves an unusually large number of potentially confounding factors in addition to nicotine inhalation. For example, there is the feel of the cigarette between the fingers, the

smell of the smoke, the smell of the unburnt tobacco, and the ritualistic lifting of the cigarette to the mouth. Scott et al. very appropriately addressed this issue by having subjects smoke de-nicotinized cigarettes during the "baseline" portion of the study, while nicotine-containing cigarettes were smoked during the challenge scanning. This assured that the same sensory properties and behaviors were present in both study conditions; ostensibly, the only difference was the presence of nicotine.

The end result of this study was a lower BP while smoking the nicotine cigarettes, with the resulting interpretation that nicotine induced dopamine release. However, there is a question of "relativity" in designs such as this, as two *behavioral* conditions are being compared. One can only make statements about the relative levels of dopamine between conditions, but inferences cannot be made about any *absolute changes* in dopamine that may have occurred during either condition. It is possibile that the "behavioral baseline" in this example is not a truly neutral stimulus. This "baseline" state involved naturally-conditioned cues of smoking; if subjects perceived that no nicotine was being delivered, it is possible that DA transmission *declined* during the baseline state [e.g., 44], and returned to basal levels during the nicotine exposure condition. A parallel interpretation could be made for Urban *et al.* [35] study, as their design used a placebo drink that was "masked" with vodka, providing some of the oral sensory properties involved with drinking. It is likely that subjects would quickly perceive that no alcohol was in the drink, especially the half of the sample who had already experienced the effects of the alcohol condition. Without a study to affirm that the "behavioral baseline" does not alter DA levels relative to a "true" resting baseline, interpreting the directionality of results may not be straightforward. That said, with PET, there are many compelling factors that would make the incorporation of a "true" resting baseline into most study designs impractical. These include the considerable cost of adding scans, and, if conducting more than two scans per subject, subject fatigue, attrition, and additional radiation exposure all may become relevant. It will not always be possible to collect data to make sure a given "baseline" or "control" condition is not different from a resting baseline scan, but it is vital that researchers carefully consider multiple interpretations of their results should they choose to forego a rest scan as the baseline comparator.

TO BLOCK OR NOT TO BLOCK (AND OTHER ALCOHOL RESEARCH DESIGN QUESTIONS)

The shared impetus for all of the RAC PET studies on alcohol-induced dopamine release was rooted in the once widely-held assumption that ventral striatal dopamine levels would behave according to the classical pharmacologic dose-response curve, that is, dopamine levels should follow blood alcohol levels. Thus, the majority of studies on alcohol-induced dopamine release involved delivering either oral [33-35] or IV alcohol [38, 39, 45] prior to PET scanning – all were classical blocking experiments as described above. The blocking experiments shared the dual goals of getting subjects to an intoxicating blood alcohol level prior to tracer injection, and then maintaining a relatively stable ethanol level (and, presumably, stable increases in dopamine levels) during the course of image acquisition in the alcohol challenge condition. In order to tightly control timing of alcohol administration, we elected to use a displacement approach in one cohort [38], starting our alcohol clamp procedure five minutes after tracer injection. The displacement approach was based on the belief that IV alcohol clamp administration would produce a robust and sustained effect on dopamine release that would result in displacement. As we found, dopamine levels do not track with brain ethanol levels [36, 37], but this *post hoc* finding does not mitigate the key point: it is important to select an optimal experimental design based on the *expected* behavior of the NT of interest during a challenge condition. In general, a well-designed blocking experiment that times the maximal free tracer concentration to coincide with peak NT concentration is expected to produce the largest effects [24]. Displacement experiments are crucial when the goal is to control stimulus timing absolutely or to characterize the *dynamics of the NT itself* [2, 46-51] (techniques for detecting temporal parameters of NT release may also require some assumptions about the temporal activity of the NT). Having a well-founded guess of NT behavior is only half the battle. As discussed above, selection of tracer is also important.

[^{11}C]RACLOPRIDE AND OTHER KEY D_2/D_3 RADIOLIGANDS

The other common feature of PET studies on alcohol-induced DA release is that they all utilized RAC, mostly with paired, single-bolus paradigms (Urban and colleagues used a paired, bolus-infusion protocol; however, the important differences across all studies were the timing and dosage of alcohol, not method of RAC delivery). Presumably, the unanimous selection of RAC was because a) all groups had *a priori* hypotheses that involved the ventral striatum as the target region of interest, and b) RAC has the distinct advantages of coming to equilibrium quickly in the striatum and being readily displaceable by endogenous dopamine. Because of these desirable properties, RAC will likely remain the tracer of choice for studies of striatal dopamine for the foreseeable future. However, research into the role of dopamine in alcohol use, abuse, and dependence need not, and should not, remain constrained to the striatum. At this writing, there are no published neuroimaging reports on extrastriatal dopamine function related to either social drinking or alcohol use disorders (AUDs). An area of potential interest would be the effects of alcohol on dopamine in the prefrontal cortex, which is an integral component in reward systems. Unfortunately, if alcohol induces dopamine release in mesocortical dopamine neurons, it is highly unlikely it would be detectable with current PET ligands. This experiment awaits a high-affinity ligand that has *both* excellent signal-to-noise properties in areas of low D_2/D_3 density and an extremely high sensitivity for displacement by endogenous cortical dopamine.

We suggest that future research on dopamine in AUDs should focus on the role of extrastriatal (and striatal) dopamine in *cognitive processes* that mediate the development and maintenance of AUDs. For future hypothesis testing of dopamine function in extrastriatal systems, high-affinity D_2/D_3 antagonists such as FAL and [^{11}C]FLB457 (FLB) should be considered. When the hypothesis concerns cortical dopamine release, the kinetics of each tracer should be bal-

anced against the goal of the study. Recent work has demonstrated that FLB has superior signal-to-noise ratio in low-density areas, but that FAL is more displaceable [23, 52, 53]. Thus, if an investigator prefers a displacement paradigm to study cortical DA release, FAL would be preferable; if a broader signal range of BP is important, a blocking study with FLB would make sense. If dopamine release is of interest in subcortical structures such as the thalamus, amygdala, and hippocampus, then FAL is likely the tracer of choice, regardless of paradigm (the short half-life of C11 (20.4 min) and tracer kinetic properties of [^{11}C]FLB457 do not permit assessment of BP in structures with even intermediate densities of D_2/D_3 receptors [53]). If an investigator wants to assess multiple dopamine systems, then FAL with a blocking paradigm would be a reasonable design. Note that these recommendations are based on the current most commonly used antagonist tracers. To our knowledge, the utility of agonist tracers for examining changes in endogenous dopamine has not been conclusively demonstrated, although a recent report suggests that the D_2 agonist [^{11}C]PHNO may be more sensitive than RAC at detecting changes in endogenous striatal dopamine [54].

ALL VOXELS ARE ROIS, BUT NOT ALL ROIS ARE VOXELS

A word on two basic approaches to data analysis is warranted to provide the reader with additional information for evaluating the literature. Studies of alcohol-induced dopamine release have used "region of interest" (ROI) approaches for analysis [33, 35, 39, 45] and "voxel-wise analysis" [34, 38]. The merits and pitfalls of each approach have been under debate, and a detailed treatment is beyond the intent and purpose of our discussion. Here, we seek to give a general explanation of the most relevant differences between the approaches for analysis of PET data. ROI analyses involve extracting an average time-activity curve from all the voxels in the ROI, and estimating BP from the mean time-activity curve. Voxel-wise analyses involve estimation of BP at each voxel within an image (or subsection of an image), essentially treating each voxel as a very, very small ROI. The resultant parametric images are typically spatially smoothed to reduce variation in BP values, which is induced by noise from the voxel time-activity curves. The ROI approach has the advantage of a more precise estimation of BP, as the average time-activity curves are typically less noisy than TACs from individual voxels. Yet a third approach is to apply an ROI to a parametric image (e.g., a BP image), and extract the average BP values from all voxels. In our experience, this hybrid of data extraction yields results almost identical to those obtained with the traditional ROI method, indicating that voxel-wise analyses with smoothed parametric images are a viable alternative. The major disadvantage of the canonical ROI method is that if relevant changes in NT levels occur only in a small, circumscribed area of an anatomically defined structure, then these effects would be effectively diluted – or even washed out completely – when the TACs of the entire structure are averaged. ROI analyses are appropriate for studies where the investigators are confident that the effect of interest is anatomically widespread across the structure of interest (e.g., amphetamine-induced dopamine release across the striatum). Voxel-wise approaches are useful when the anatomical across the striatum extent of a hypothesized effect is unknown, and for exploratory analyses. A voxel-based analysis also has the additional advantages of avoiding labor-intensive region drawing, and does not suffer from investigator-induced bias in definition of anatomic structures. Ultimately, ROI and voxel-wise analyses can provide complementary information.

SUMMARY

While most of the examples given in this conceptual review are specific to the field of alcohol research, the considerations are universal when researchers endeavor to use neuroligand PET to further our knowledge about the neurochemistry of cognition and behavior. A basic understanding of tracer kinetics, ligand properties, and factors that affect data outcomes and interpretation is crucial for even the most elemental of studies that probe neurotransmitter function.

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