offering valuable guidance for selecting or refining these techniques. These important approaches, based on the competition model, assume that the radiotracer competes with endogenously released neurotransmitter for postsynaptic receptor binding. Notably, the model is subject to a ceiling effect at about a 40% signal change, even for pharmacologic stimulation, for which neurotransmitter release may exceed 1,000%. Cognitive paradigms typically yield smaller signal changes (5%–15%).

As the work aimed to represent the state of the art (*4*), it is worth highlighting recent developments in functional PET (fPET) imaging. fPET uses repeated stimulation, which is isolated from baseline radiotracer uptake (*5*). Initially developed to image stimulation-induced changes in glucose metabolism with [^{18}F]FDG, fPET has recently been adapted to the dopamine and serotonin neurotransmitter systems (*6,7*). The synthesis model underpinning fPET leverages the fact that neurotransmitter release is coupled with the corresponding synthesis process to replenish synaptic vesicles with de novo synthetized neurotransmitter. As the technique is still developing, the numeric relationships between neurotransmitter release and synthesis changes observed with fPET still need to be established. Also, current modeling is relatively simple, assuming a linear stimulation-induced increase in the time–activity curve, modeled with the general linear model and quantified with the Patlak plot. Nevertheless, this approach has proven particularly robust across various radiotracers and stimulation paradigms, with signal changes reaching about 100% for 6-[^{18}F]FDOPA (*7*) and about 40% for [^{11}C]AMT (*6*). Additionally, the high temporal resolution of fPET (seconds) supports the computation of molecular connectivity (*8,9*), which examines within-subject regional associations of PET dynamics rather than static, between-subject covariance. The simplicity of the technique, the strong signal changes, and the recently introduced fPET toolbox (*10*) together make fPET an accessible and effective approach for studying neurotransmitter dynamics, offering researchers easy and standardized access into this emerging field.

In conclusion, both the competition model and the synthesis model are pivotal for investigating neurotransmitter response. Although the former substantially benefitted from decades of refinement (*4*), emerging developments in fPET promise to expand the synthesis model's capabilities, enabling a more detailed characterization of neurotransmitter signaling. Integrating these 2 approaches could further provide complementary perspectives, enriching our understanding of neurotransmitter dynamics.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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Published online Mar. 13, 2025.
DOI: 10.2967/jnumed.124.269238

REPLY: We are pleased that Lanzenberger et al. have drawn attention to our recent review, "Modeling PET Data Acquired During Nonsteady Conditions: What If Brain Conditions Change During the Scan?" (*1*). We are further pleased that our colleagues are advancing methods to push boundaries to find new and more powerful ways to use PET imaging and to explore stimulation-induced changes in the brain. We support it. The letter by Lanzenberger et al. provides us the opportunity to drill down into some important points about transients and the relative strengths of methods.

What is meant by transient? And why is it important? The main focus of our paper was to review and discuss the development of models that include *explicit* mathematical terms that describe transient phenomena, such as the release of a neurotransmitter in response to a short-lived external stimulus. A transient occurs in the transition from one steady state to another. To describe transients mathematically, we use functions that are time-varying. Thus, the difference between the methods we described in our review and the functional PET (fPET) method the letter-writers refer to is this: The various models detailed (linear simplified reference region model, linear parametric neurotransmitter PET [lp-ntPET], etc.) attempt to describe the dynamics of the neurotransmitter *during* the transient event and its effect on the PET signal *during* the transient. fPET, on the other hand, seeks to *detect* the transition and quantify a difference between 2 states but not to characterize what is happening during the change from one state to another of the PET signal or of the neurotransmitter that caused it.

Does the distinction matter? We believe it does. There are as yet untested hypotheses in the literature that suggest that the tran-

sient feeling of "high" is comparable in speed and progression (i.e., curve shape) to the transient dopamine elevation after drug-taking. Thus, it has been speculated that "high" is *encoded* in the transient dopamine elevation and subsequent return to baseline (*2,3*). Similarly, there is evidence that reward prediction error during conditioned learning is related to, and thus encoded by, transient dopamine signals (*4*). And, it is hypothesized that the reward prediction error apparatus is disrupted in schizophrenia (*5*). In both cases, modeling the transient explicitly (i.e., the time of onset, the peak, and the return to baseline), rather than just detecting it, matters.

What is meant by temporal resolution? In practical terms, it is the ability of a system to resolve distinct phenomena in time. It is not the same as sampling frequency. We have previously established that the practical temporal resolution of lp-ntPET (given a certain realistic sampling frequency, a signal-to-noise ratio, and a particular model) is between 3 and 8 min (*6,7*). That is, we can reasonably expect to be able to distinguish between one transient dopamine response that peaks 2 min after a stimulus commences (e.g., cigarette smoking) and another one that peaks 7 min after the start of stimulus. Another one of our studies demonstrated that, with additional postprocessing of parametric images, we can reliably differentiate voxel locations tied to an early event from voxel locations tied to a late event (*8*). In yet an older experimental study, we used another variant of our models (*9*) (also cited in the review paper) to distinguish between 2 different finger-tapping epochs and correctly classify them as having occurred 15 min apart (*10*).

Whatever the *practical* temporal resolution of fPET, it is not seconds, as claimed. Practical temporal resolution can improve with improvements in scanner sensitivity, but as with our work on lp-ntPET and related techniques, the practical temporal resolution can only be established through analysis of simulations and experiments.

What is meant by a ceiling effect? That is, what are the concerns when using a saturable phenomenon as the measurable signal in any assay? The answer must be organized into 2 parts:

1. Virtually all biologic phenomena are enzyme- or receptor-mediated. All such phenomena are governed by the potential saturation of limited numbers of enzyme- or receptor-binding sites. Biology makes no distinction between a receptor that binds dopamine or an enzyme that synthesizes it. Saturation by itself does not negate the value of a signal, nor does it even undermine its quantifiability. It simply means that the relationship between the input (a drug or a behavioral stimulus) and its measured output (a change in tracer binding to a receptor) is nonlinear.

   What is an investigator to do with a saturable signal? Either configure the experiment to remain squarely in the linear range of the input-output relationship, or apply the appropriate *nonlinear* model to describe the output as a function of the input. In occupancy studies with PET, the application of Emax models is an example of the latter. In effect, with lp-ntPET and like models, we do both—use nonlinear models and restrict their applicability. Can we use lp-ntPET or other models to differentiate between 2 extreme dopamine levels, both of which cause total blockade of all D2 receptors? No. But in most circumstances, that is not particularly interesting or relevant. All investigators would be well advised that whatever phenomenon they are detecting, it is also likely saturable. Only once one performs a dose–response study can one assess whether saturation has any practical effect on the ability to detect what one cares about.

   Cognitive paradigms are where it's at. And as stated by the letter-writers, cognitive paradigms yield small signal changes. That is where the field is going—not to detect differences in the effect of 1 truckload of amphetamine versus that of 2 truckloads, but rather to detect and characterize the responses to subtle behavioral and cognitive challenges.
2. From where does the claim of a ceiling effect of 40% signal change come, and what does it mean for the utility of binding potential? This is worth addressing—and laying to rest. The observations, originally published as early as 1997 (*11,12*), report that the change in binding potential (ΔBP) of raclopride in response to large doses of amphetamine tops out at 40%. This has somehow been enshrined in the PET literature as a demonstration of a fatal weakness of ΔBP as a measure of neurotransmitter response, broadly.

   First, consider the above arguments about the use of linear versus nonlinear signals. Second, we must always be mindful of what binding potential is. It is a constant and not a function of time. Thus, it only truly applies to the description of a system at steady state. In turn, the assumption, when using ΔBP to assay for the effect of a dopaminergic drug, is that synaptic dopamine level transitions abruptly from one steady state (baseline) to another state (drug-induced) where it remains for the duration of the scan or extended measurement period. This is a very restrictive idealization. Transitions happen over finite amounts of time and have varied arcs. The ramifications of applying ΔBP when the system does not jump instantaneously or consistently from one steady state to another, or worse, when a second steady state is never reached, have been well studied and explained by Yoder et al. (*13*) and Sullivan et al. (*14*) and reprised in our review. Any PET user who persists in defying prevailing assumptions of an analysis method must proceed at his or her own risk.

In summary, models such as lp-ntPET using an explicit transient term do not labor under the assumption of instantaneous transition between steady states. Rather, they embrace the transition and model it. Used appropriately, they can uncover important patterns and phenomena that have direct relevance to the neurobiology of reinforcement learning and drug addiction and that have, heretofore, been largely ignored by the PET research community. Naturally, we welcome all new techniques that have the potential to extract more information from dynamic PET data. To characterize transient neurotransmitter responses to drugs and behavior, however, the class of models and techniques catalogued in our recent review paper are the current best efforts to do so.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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Published online Mar. 13, 2025.
DOI: 10.2967/jnumed.125.269473