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Simultaneous PET-MRI Confirms That Cerebral Blood Flow Does Not Confound PET Neuroreceptor Activation Studies

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ABSTRACT: Positron emission tomography (PET) and endogenous competition paradigms are widely used for studying neuroreceptor activation in humans in vivo. Critical aspects of this changes in cerebral blood found triggered by the experimentation, such as amphetamine administration, could influence both tracer delivery and washout, thus biasing the results. A recent study tested this assumption in baboons by measuring of radiotracer binding with PET while measuring cerebral blood flow with arterial spin labeled functional magnetic resonance imaging. Cerebral blood flow was modulated by CO_2 inhalation. Hypercapnia led to substantial alterations in blood flow with no detectable alteration in binding of the reversibly binding radiotracers [^{11}C]raclopride and [^{18}F]fallypride. These results rule out a serious confound for the endogenous competition paradigm, and demonstrate the importance of simultaneous PET and MRI measurements when studying brain function.

KEYWORDS: *Neuroreceptor, dopamine, positron emission tomography, blood flow, arterial spin labeling*

MEASURING BRAIN ACTIVATION WITH POSITRON EMISSION TOMOGRAPHY

In the late 1980s, measuring cerebral blood flow (CBF) changes associated with neuronal activity with positron emission tomography (PET) and [^{15}O]-H_2O stood as the state-of the art method for quantifying brain function and mapping the functional localization of motor, cognitive, and emotional processes in the brain. This approach was soon mostly replaced by the development of the blood-oxygenation dependent (BOLD) contrast imaging for functional MRI by Ogawa and colleagues in the 1990s. Even though BOLD signal has a complex relationship with actual neuronal spiking, the fact that [^{15}O]-H_2O PET provides quantitative measurement of CBF was not enough to motivate the use this approach in "activation" studies of global neuronal activity, given its complexity, financial costs, and invasiveness.

Yet up to date, PET remains the only available technique for whole-brain in vivo measurement of the availability and displacement or activation of specific neuroreceptors. Whereas BOLD contrast imaging yields an overall index of brain activation irrespective of the involved neurotransmitters, high molecular resolution of PET makes it a preferred tool for quantifying activation of specific neuroreceptor and transmitter systems. In this kind of activation or "challenge" studies (Figure 1A), neuroreceptor availability is measured under two conditions: Once during a baseline and once during or immediately after a pharmacological or behavioral challenge, such as amphetamine administration or pain stressor. The radioligand is assumed to compete with the endogenous radioligand for occupancy at the neuroreceptors, hence altered endogenous neurotransmitter levels can be measured by monitoring changes in the radioligand binding with the PET camera.

POTENTIAL EFFECTS OF BLOOD FLOW ON NEURORECEPTOR ACTIVATION STUDIES

This endogenous competition (challenge) paradigm has several potential confounds, of which changes in CBF is perhaps most often cited. Critically, many challenges typically administered in receptor activation studies, such as amphetamine administration,[1] or physical exercise[2] most likely lead to significant changes in CBF, thus raising doubts about the interpretation of the effects of challenges studies. Such alterations in CBF could potentially influence both delivery and washout of the tracer, leading to artifactual changes in binding potential estimates. Theoretically, the simplified reference tissue model (SRTM) used for many radioligands used in challenge studies (such as [^{11}C]raclopride and [^{11}C]carfentanil) should control for potential effects of blood flow, as the outcome measure, specific to nondisplaceable binding potential (BP_{ND}), would correct for both changes in peripheral delivery and differences in arterial input function. Additionally, simulation studies suggest that the effect of CBF on neuroreceptor activation studies with reversibly binding radiotracers would be negligible,[3] and analysis of k_2 images derived using SRTM (reflecting radiotracer delivery from tissue to blood) suggest that changes in BP_{ND} are typically observed in the absence of k_2 changes.[2,4] Nevertheless, all these counterarguments are based on indirect evidence and due to methodological limitations, PET challenge studies have been done for years without directly validating the challenge paradigm with respect to perfusion-related confounds.

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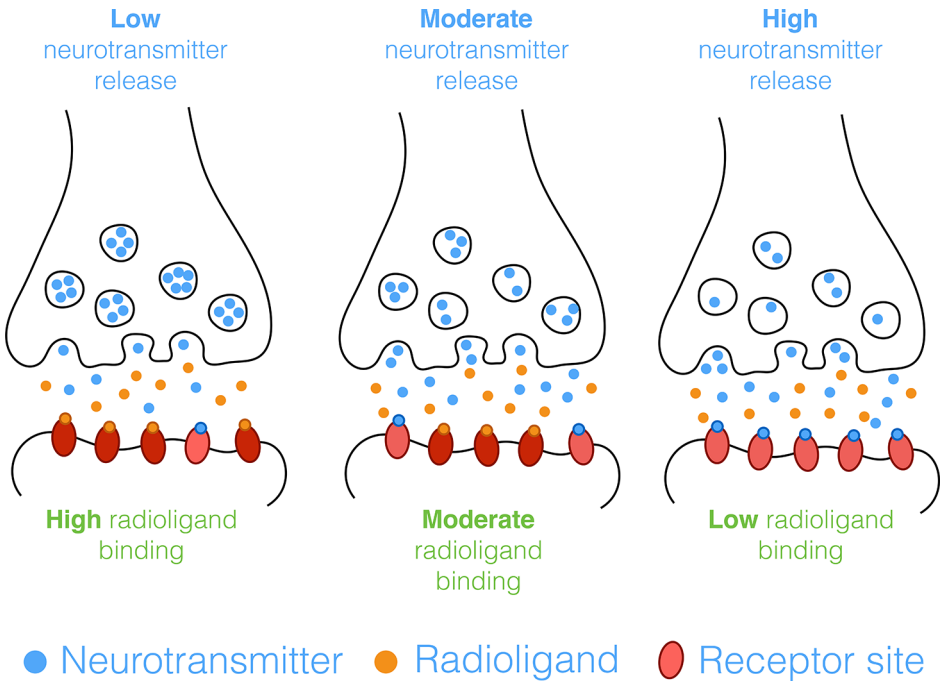

Figure 1. Illustration of the occupancy challenge paradigm. Radioligand competes for occupancy with the endogenous ligand (neurotransmitter), and thus, changes in radiotracer binding are assumed to be (not necessarily linearly) proportional to endogenous ligand in the synaptic gap.

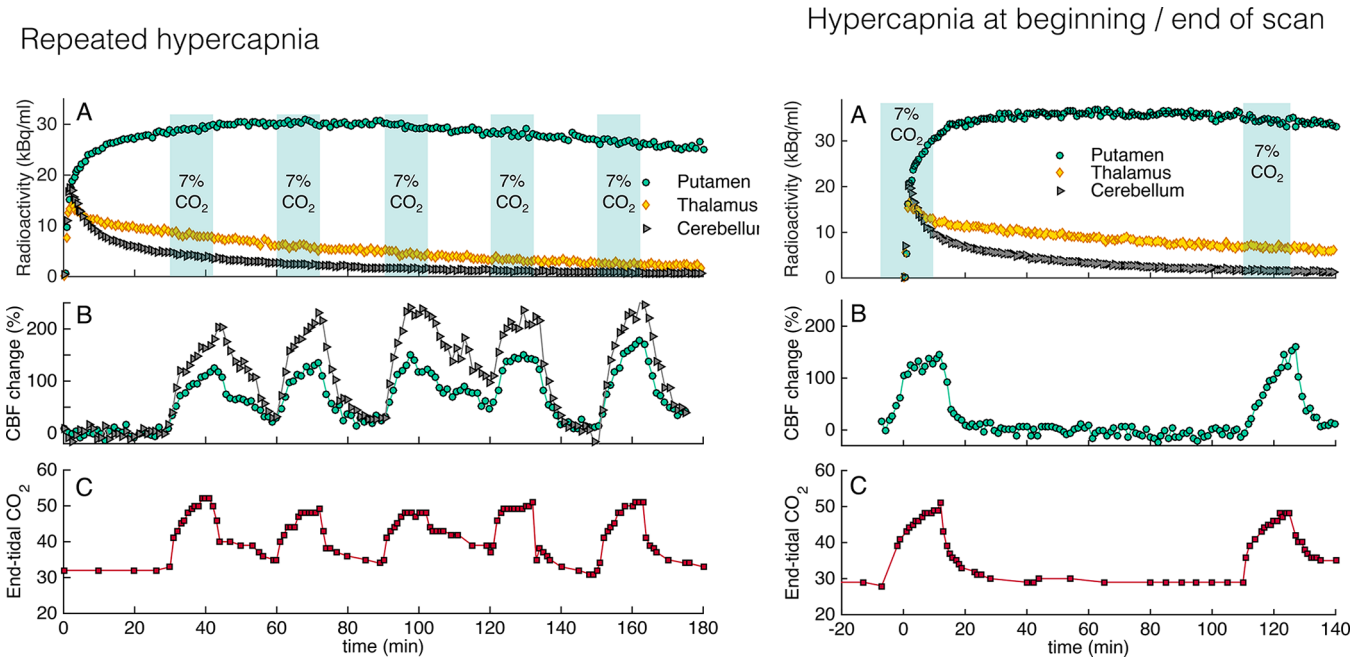

Figure 2. Main findings from ref 5 from the repeated (left) and two-shot hypercapnia conditions (right). Top row: [^{18}F]fallypride radioactivity. Middle row: CBF change measured with ASL-fMRI. Bottom row: End-tidal CO_2. Sander, C. Y., Mandeville, J. B., Wey, H.-Y., Catana, C., Hooker, J. M., and Rosen, B. R. *Journal of Cerebral Blood Flow and Metabolism* (in press). Copyright 2017 by the Authors, Reprinted by Permission of SAGE Publications, Ltd.

SIMULTANEOUS MEASUREMENT OF PERFUSION AND NEURORECEPTOR ACTIVATION IN A NONHUMAN PRIMATE MODEL

The advent of PET-MRI allows simultaneous measurement of brain perfusion (with arterial spin labeled MRI) and radioactivity uptake after tracer injection (with PET), and thus provides the current gold standard method for conclusively resolving this issue. Recently, Sander and colleagues provided the first direct in vivo quantification of the relationship between tracer uptake and blood flow in the primate brain.[5] In an elegantly designed PET-MRI study, they scanned two baboons with PET using two well-validated reversibly binding radiotracers with different pharmacokinetics: [^{11}C]raclopride and [^{18}F]fallypride, both labeling brain dopamine D_2 receptors. During the PET scan, cerebral blood flow was measured continuously using arterial spin labeled MRI. A hypercapnia challenge with 7% CO_2 was administered

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repeatedly during the scan to induced change in CBF, and also separately at the beginning and at the end of the scan. This allowed testing whether radioactivity uptake would be confounded by concomitant hypercapnia-induced changes in perfusion.

As expected, hypercapnia increased CBF by about 2.5-fold, which coincided with increased end-tidal CO_2. Importantly, increased perfusion occurred without any noticeable concomitant change in uptake of either radiotracer binding (Figure 2). Radioligand binding was unaltered regardless of whether increased perfusion occurred before or after equilibrium of radioactivity uptake. To date, this pattern of findings represents the most reassuring demonstration of the independence of reversible radiotracer binding and brain perfusion, providing reassurance that prior work using the challenge paradigm were not likely confounded by altered perfusion. This study also demonstrates the power of simultaneous PET-fMRI measurements; this type of study would not have been possible by other means, such as consecutive measurements of perfusion and radiotracer binding.

OUTSTANDING QUESTIONS

The convincing nature of the results notwithstanding, several questions remain open. First, it must be noted that the simultaneous PET-fMRI paradigm of Sander and colleagues rely on delivering the hypercapnia challenge and the control condition within a single PET scan, without a fully independent control scan. Thus, one could question the sensitivity of PET for picking up short-term hyperperfusion-induced changes within such design. Also, we do not know how well these results translate to the different approaches and methods are being used for PET displacement studies. We and others favor the simple single-bolus injections with single scan per condition, while some employ a bolus injection followed by continuous radiotracer infusion to achieve steady-state radioligand binding. Although, the relative sensitivity of these approaches to blood flow remains to be tested, the fact that even very large blood flow changes produced no measurable changes in the PET data reassures that blood flow does not affect the quantification of these tracers.

The degree to which these results are generalizable to other radiotracers also remains unknown. Displacement studies typically employ reversibly binding radioligands, such as [^{11}C]raclopride and [^{18}F]fallypride assessed here. Because even these two radioligands have very different pharmacokinetics, these results likely translate to other reversibly binding radioligands as well. Another remaining question in this context is how well these nonhuman-primate results translate to humans. Yet, given the bulk of evidence from simulations and observation from human PET data up to date,[3] we think these results can safely be assumed to hold in humans as well.

All in all, these results are reassuring to the PET researchers using the challenge paradigm, ruling out one of the most widely speculated confound of altered CBF. This work elegantly shows what simultaneous PET-MRI imaging is capable of, and likely opens new venues for linking neurotransmitter function with MR-based indexes of neuronal activity.

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Notes

The authors declare no competing financial interest.

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