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Recent Developments in Molecular Brain Imaging of Neuropsychiatric Disorders

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Molecular imaging with PET or SPECT has been an important research tool in psychiatry for as long as these modalities have been available. Here, we discuss two areas of neuroimaging relevant to current psychiatry research. The first is the use of imaging to study neurotransmission. We discuss the use of pharmacologic probes to induce changes in levels of neurotransmitters that can be inferred through their effects on outcome measures of imaging experiments, from their historical origins focusing on dopamine transmission through recent developments involving serotonin, GABA, and glutamate. Next, we examine imaging of neuroinflammation in the context of psychiatry. Imaging markers of neuroinflammation have been studied extensively in other areas of brain research, but they have more recently attracted interest in psychiatry research, based on accumulating evidence that there may be an inflammatory component to some psychiatric conditions. Furthermore, new probes are under development that would allow unprecedented insights into cellular processes. In summary, molecular imaging would continue to offer great potential as a unique tool to further our understanding of brain function in health and disease.
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Introduction

In vivo imaging of brain neurochemistry with PET or SPECT has been used in psychiatry research as these tools became available, and continues to be a widely used methodology for gaining insight into the neuropathology of psychiatric conditions. Seminal studies examined receptor and transporter availability, demonstrated target engagement by drugs, and provided evidence of dysregulated neurotransmission. The methodological principles established by these early studies continue to provide the framework for ongoing research, albeit with considerable refinement and expansion of the approaches to analysis, the molecular targets, and the imaging probes available. Here, we examine two areas of particular interest in psychiatric neuroimaging. Following a brief introduction to commonly used outcome measures, we discuss approaches to making inferences about neurotransmission using imaging, from the inception of these methods through recent developments and refinements. Next, we examine the methodology and recent results for imaging neuroinflammatory markers, a branch of brain imaging that has an extensive literature in the context of other conditions but has more recently become of interest in psychiatry, owing to accumulating evidence suggesting a role of inflammation in psychiatric conditions.

Methodological considerations

Many of the tracers used in psychiatric imaging bind reversibly to their target molecules. To extract biologically relevant parameter values, data are fitted to mathematical models, frequently referred to as compartment models, that combine equations for transport across the blood-brain barrier with mass action laws governing the association and dissociation of the tracer with its target. Compartment models have been reviewed in detail elsewhere,[1-3] but the most relevant outcome measures are described briefly here. These are binding potentials (BP) and distribution volumes (V). Both represent ratios of the concentrations of different pools, or compartments, of the radioligand to each other at equilibrium, but can also be expressed in terms of pharmacokinetic parameters. BP is proportional to the equilibrium ratio between the

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concentration of radioligand specifically bound to its target and unbound, or free, tracer. It can also be represented as proportional to the product of the target density and the affinity of the radiotracer for the target, or B_{avail}/K_D, where B_{avail} is the concentration of target available for binding to the radioligand and K_D is the equilibrium dissociation constant of the reaction. The constant of proportionality depends on how the free tracer is represented in the model, but the most frequently reported version is $BP_{ND} = f_{ND}B_{avail}/K_D$, where f_{ND} is the free fraction of free and nonspecifically bound radiotracer (the nondisplaceable compartment) in brain tissue. If the free concentration is measured in arterial plasma, the constant is f_p, the portion of tracer not bound to plasma proteins, and the binding potential is $BP_P = f_pB_{avail}/K_D$. If f_p is measured and corrected for, the constant is 1 and the binding potential is $BP_F = B_{avail}/K_D$. Below, we will use the specific forms when referring to studies in which they were used, and the generic BP for properties that apply equally to all versions. The equilibrium ratio of the nondisplaceable compartment to arterial plasma is V_{ND} and is usually assumed to be equal throughout the brain. The equilibrium ratio of all tracer in a brain region to the arterial plasma concentration is V_T, the total distribution volume, $V_T = V_{ND} + BP_P$. Reliable methods of deriving BP usually require either an estimate of V_{ND} that can be subtracted from V_T, or use of a reference tissue model in which a direct relationship is formed between the target-rich region and a region with negligible concentration of the target molecule (the reference tissue). V_{ND} can be estimated either by measuring it in the reference tissue or by performing separate pharmacologic blocking experiments. When none of these options are available but radiotracer concentration in arterial plasma is measured, V_T can be used to make inferences about neurotransmission, although it differs from proportionality to the target concentration by the constant V_{ND}.

Importantly, the radioligand is usually administered at tracer dose, a concentration too low to occupy more than a small percentage of the target molecules. The net effect is that inferences about target occupancy by endogenous or exogenously administered ligands are independent of radiotracer concentration. In particular, fractional changes in BP following experimental manipulations that cause changes in concentrations of competing ligands can be interpreted solely in terms of the properties of the competing ligand.

Neurotransmission Imaging

A general approach to imaging neurotransmission is to assess BP under a baseline condition and then again following a perturbation of the system. Inferences are made by calculating the percentage change, ΔBP, of the binding potential. An essential requirement is the fact that the binding is sensitive to changes in the concentration of endogenous ligand, a property that is not observed for all radiotracers. If the perturbation increases the concentration of the endogenous transmitter at the level of the target receptor and the tracer and the transmitter compete for the same binding site, ΔBP would be a proxy for receptor occupancy by the transmitter. In reality, the interaction may be more complicated than pure competition, involving other phenomena such as receptor trafficking or the contribution of baseline receptor occupancy by the transmitter. Still, at least for some systems, validating studies have been performed showing clear dose responses between measured endogenous transmitter release and the magnitude of ΔBP. If the perturbation depletes endogenous transmitter, ΔBP would be indicative of the baseline level of transmitter, and under the assumption of complete or near-complete depletion, ΔBP/(1 + ΔBP) provides an estimate of baseline receptor occupancy. If the tracer binds to an allosteric site, changes in the level of endogenous transmitter would affect the affinity, $1/K_D$; theoretical predictions suggest that increased transmitter levels should decrease BP of allosteric antagonist radiotracers and increase BP of allosteric agonists, although again, other processes such as receptor trafficking may come into play. Finally, in some cases, metabolism radiotracers that partially follow the same metabolic pathway as the precursor to the endogenous transmitter have been used to make inferences about transmitter synthesis and storage capacity. Here, we discuss neurotransmitter imaging as it relates to imaging applications in psychiatry. In some cases, this involves paradigms that have been in use for years to study psychiatric populations. In others, the methods are just being developed or have been less successful despite much research.

Dopamine

Dopamine Transmission: Transmitter Release and Reuptake Blockade

The most robust paradigms for imaging dopamine transmission have been the combination of D2/D3 receptor radiotracers with pharmacologic challenges such as D-amphetamine that extrudes dopamine from synaptic vesicles and releases it through reversal of the dopamine reuptake transporter,[4] or methylphenidate that blocks the reuptake transporter, causing accumulation of dopamine released via synaptic transmission.[5] The approach was also tested with D1 receptor radioligands[6] without success. However, D2/D3 tracers produced clear results and have been used in release and reuptake blockade paradigms. In the 1990s, studies used the SPECT D2/D3 radiotracer [^{123}I]IBZM in combination with amphetamine,[7] or the PET D2/D3 radiotracer [^{11}C]raclopride with either amphetamine[8] or methylphenidate[9] to examine dopamine transmission in the striatum. Using [^{123}I]IBZM, it was shown that amphetamine-induced dopamine release was higher, on average, in unmedicated patients with schizophrenia than matched controls, and that the magnitude of release was correlated with the level of symptom exacerbation in patients,[10] an observation that fits well with the fact that virtually all antipsychotic drugs block a substantial portion of dopamine binding to D2 receptors. Similar results were obtained independently using amphetamine in combination with PET and [^{11}C]raclopride.[8] Studies in nonhuman primates correlating these results with microdialysis measurement of dopamine levels showed a dose response to amphetamine of both dopamine levels and the magnitude of ΔBP,[11] but also