The Application of Neuroimaging Techniques to Drug Development

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Neuroimaging is a powerful and innovative tool for studying the pathology of psychiatric diseases and, more recently, for studying the drugs used in their treatment. Technological advances in imaging have made it possible to noninvasively extract information from the human brain regarding a drug's mechanism and site of action. Until now, our understanding of human brain pharmacology has depended primarily on indirect assessments or models derived from animal studies. However, the advent of multiple techniques for human brain imaging allows researchers to focus directly on human pharmacology and brain function. This review outlines available neuroimaging techniques and examines how these various methods have already been applied to the drug development process, as well as how they might be applied in the future. *(J Clin Psychiatry 1997;58[suppl 10]:3–6)*

NEUROIMAGING TECHNIQUES

Human brain imaging describes a family of radiologic procedures, including structural, functional, and neurochemical techniques, that have been introduced over the past decade. Initially, imaging studies were designed rather exclusively to study the pathophysiology of neuropsychiatric disorders, rather than to characterize drug effects within the brain.[1–5] Therefore, the full potential of these techniques for increasing our understanding of neuropharmacology has yet to be realized.

Neuroimaging techniques are classified into three groups—structural, neurochemical, and functional—based on the type of information they provide. Structural imaging techniques, including *computerized tomography* (CT) and *magnetic resonance imaging* (MRI), have revealed subtle changes in certain neuropsychiatric diseases,[3,6,7] but are less well suited to drug development studies. As a consequence, a more detailed discussion of these techniques is beyond the scope of this review. Neurochemical and functional neuroimaging methods, on the other hand, represent very useful techniques for evaluating drug activity in the brain. Neurochemical imaging, which utilizes *positron emission tomography* (PET), *single photon emission computerized tomography* (SPECT), and *magnetic resonance spectroscopy* (MRS), encompasses a group of techniques that are particularly effective for visualizing and quantifying the regional distribution of specific drugs. Neurochemical techniques can also describe drug effects on specific neurotransmitters and their receptors. Functional imaging, which utilizes PET, SPECT, and *functional MRI* (fMRI), has been applied to drug development even less frequently than neurochemical imaging. However, the information provided by functional imaging (i.e., localizing, as well as quantifying, drug activity) may be even more useful. Examples of how these two families of techniques can generate useful information for the drug development process are summarized below.

NEUROCHEMICAL IMAGING

Despite the obvious utility of neurochemical methods for localizing drug action, only a limited number of studies using these techniques have been completed to date. In neurochemical imaging studies, PET and SPECT are used to measure the in vivo binding profile of a radiolabeled form of a drug binding to a clinically relevant receptor population. For example, using PET, it is possible to compare the in vivo binding characteristics of two distinct opiate receptor ligands, carfentanil and buprenorphine. PET studies by our group localized the binding of ^{11}C-carfentanil, a μ receptor agonist, to sites in the thalamus and amygdala. In contrast, ^{11}C-buprenorphine, which binds to μ, κ, and δ receptors, labels sites in the cortex and basal ganglia, as well as the μ receptor population labeled by carfentanil. This illustrates the usefulness of PET for comparing in vitro binding data with receptor binding specificity in the human brain. PET imaging is also a valuable tool for examining receptor occupancy in vivo. Displacement studies, for example, can be used to further

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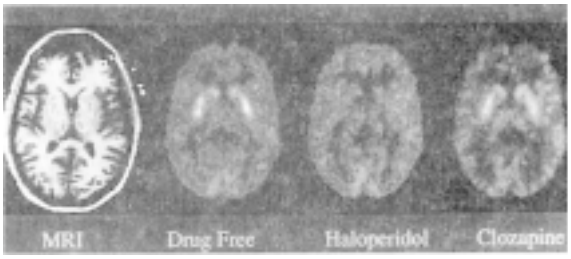
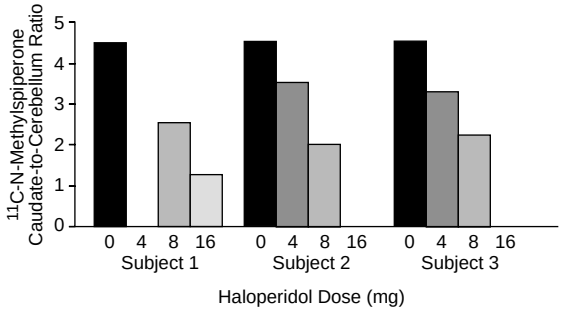
Figure 1. ^{11}C-NMSP Receptor Occupancy: Classical Versus Atypical Neuroleptics*



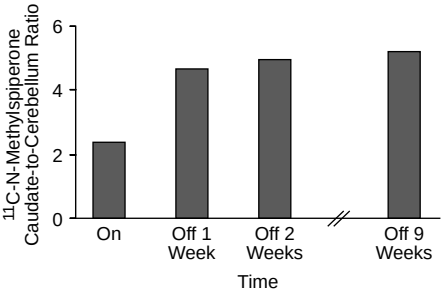
*From reference 13, with permission. Transaxial images obtained by PET scanning with ^{11}C-N-methylspiperone (^{11}C-NMSP) as the receptor ligand.
Drug free = baseline image following 2 weeks off medication;
Haloperidol = image after 4 weeks on haloperidol (30 mg/day);
Clozapine = image after 4 weeks on clozapine (450 mg/day).

Figure 2. Displacement of ^{11}C-NMSP by Haloperidol: Dose-Response*



*From reference 17, with permission. Ratio of ^{11}C-N-methylspiperone binding density in caudate nucleus: cerebellum after haloperidol (4–16 mg) or saline, as determined from PET images.

Figure 3. Haloperidol Withdrawal: ^{11}C-NMSP Binding*



*From reference 17, with permission. Ratio of ^{11}C-N-methylspiperone binding density in caudate nucleus: cerebellum after discontinuation of haloperidol, as determined from analysis of PET images.

clarify the binding profile of a ligand labeling multiple receptors in vivo. Such studies have been crucial to neuroradiologic investigations of schizophrenia and dopamine receptors.[1–5,7–10] ^{11}C-N-methylspiperone (^{11}C-NMSP) has been the receptor ligand used in many of these studies. A high-affinity dopamine receptor antagonist, ^{11}C-NMSP binds primarily to sites within the striatum, but also binds in the cortex to serotonin 5-HT$_2$ receptors. Previous imaging studies have shown that ^{11}C-NMSP binding in the striatum can be blocked by haloperidol, primarily due to blockade of dopamine D$_2$ receptors.[9,11,12] Our group used this observation to design a PET study comparing the receptor occupancy of a classical neuroleptic (haloperidol) and of an atypical neuroleptic (clozapine); the results of this study are illustrated in Figure 1.[13] Seven neuroleptic-free patients, maintained off medication for 2 weeks prior to a baseline scan, exhibited a high level of ^{11}C-NMSP binding in the striatum and cortex. Patients then received haloperidol for 4 weeks, which blocked most of the ^{11}C-NMSP binding in the striatum, but not in the cortex, indicating that haloperidol occupies a high percentage (85%–90%) of D$_2$ receptors in the striatum and very few 5-HT$_2$ receptors in the cortex. The patients were then transferred to clozapine for 4 weeks. PET scanning at the end of this period revealed a dramatically different profile of ^{11}C-NMSP binding, with only a 20% occupancy of the D$_2$ receptors by clozapine, but significant occupation and displacement of binding sites in the cortex, suggesting that clozapine has an in vivo preference for cortical 5-HT$_2$ receptors. These findings are similar to other reports.[8,14–16]

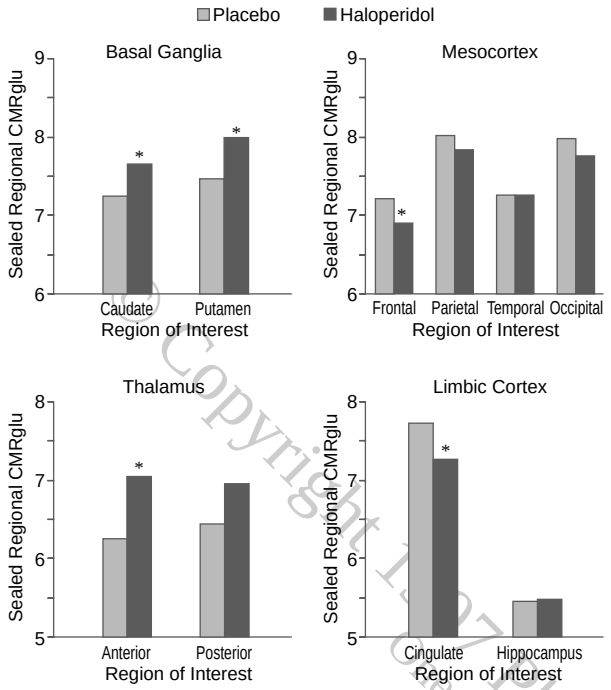
Displacement techniques have also been used to study drug dose-receptor occupancy relationships with common neuroleptics. A displacement study of ^{11}C-NMSP binding using progressively higher acute doses (0–16 mg) of haloperidol in three patients is shown in Figure 2.[17] Each patient was drug-free for 4 weeks prior to the study and was scanned weekly for 4 weeks. All three patients showed a nearly linear dose-displacement relationship between increasing dose and decreasing receptor occupancy at the D$_2$ receptor. This suggests that a steady-state dose-occupancy curve could also be generated following chronic treatment to determine if binding characteristics are both dose and duration dependent.

We have also studied elimination curves of haloperidol using ^{11}C-NMSP binding and PET to determine how long neuroleptics remain at the receptor in brain following discontinuation (Figure 3).[17] Our preliminary withdrawal data suggest that up to 2 weeks are needed to completely clear haloperidol from the brain. This is an important finding to consider when planning patient studies, changing therapies, or interpreting PET studies involving patients previously treated with neuroleptics.

FUNCTIONAL IMAGING

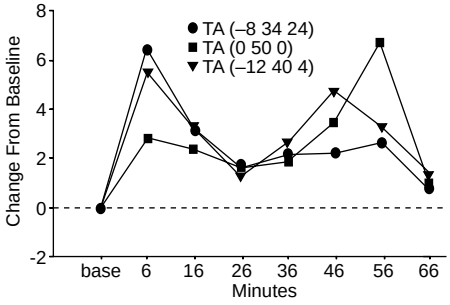
In addition to pharmacologic and pharmacokinetic questions about neuroleptics that can be addressed with imaging, it is also important to understand the functional consequences of neuroleptic administration in different brain regions. Functional PET studies of neuroleptic activity within the brain involve measuring cerebral glucose utilization with [^{18}F]-fluorodeoxyglucose (FDG) or cere-

Figure 4. Functional Consequences of Haloperidol Administration†



†Data from reference 11, with permission. Cerebral glucose utilization in four brain regions, as determined by PET-FDG after 1 month of haloperidol treatment or placebo.
*p < .05.

Figure 5. Effect of Ketamine on rCBF in Anterior Cingulate Cortex: Change Over Time of Three Significant Maxima



*TA = Talairach atlas.

bral blood flow with ^{15}O-labeled water ($H_2{}^{15}O$). In a recent study by our group, we compared within-subject PET-FDG scans in subjects after a month of haloperidol treatment and after a month on placebo.[11] We found regionally selective changes in cerebral glucose utilization between the two sets of scans (Figure 4). Increases were found in the basal ganglia and anterior thalamus with neuroleptic treatment, indicating that haloperidol enhances glucose utilization in these areas. Haloperidol also suppressed glucose utilization, but only in the frontal and cingulate cortices. Remarkably, haloperidol altered cerebral glucose utilization in areas that lack or have low densities of dopamine receptors (i.e., thalamus and cortex). Thus, we propose that the changes in the thalamus and cortex are due to secondary influences of haloperidol mediated through the drug's primary site of action in the basal ganglia, via the striato-thalamocortical pathways. Obviously, this demonstrates that important drug effects can be secondary, or even tertiary, effects that are downstream from the proposed primary site of action.

Another functional PET technique involves the measurement of regional cerebral blood flow (rCBF) using $H_2{}^{15}O$. This technique is particularly well suited to studies of short-acting psychoactive compounds because the ^{15}O isotope has a short half-life that allows for sequential scans every 10 minutes. One example of application of this procedure has been in vivo analysis of the action of ketamine, a psychoactive compound that can activate and exacerbate psychotic symptoms in schizophrenic patients.[18,19] Examining the time course of ketamine effects on rCBF in schizophrenic patients can define brain areas that may mediate acute exacerbations of psychosis. Recently, we have shown that ketamine, given in subanesthetic doses (0.1–0.5 mg/kg) to schizophrenics and controls, alters the normal pattern of rCBF.[18] Increases in rCBF are seen in the anterior cingulate and right medial frontal cortex, while decreases are observed in the hippocampus, primary visual cortex, and cerebellum. To further understand the dynamics of the changes in rCBF in the anterior cingulate cortex, we determined three areas of maximal change and plotted their relative blood flow over time (unpublished data) (Figure 5). Interestingly, the dramatic initial effect of ketamine fades away almost completely by 30 minutes, but reappears 15–25 minutes later before dissipating. In the cerebellum, a similar pattern of decrease was seen, with an initial decrease that returned toward baseline followed by a secondary decrease. Other brain regions—e.g., the inferior frontal gyrus, the precuneus region, and the post central gyrus—also displayed a unique pattern of significant blood flow changes. Thus, the ketamine-induced changes in rCBF are regionally specific, not global changes. These temporal and spatial changes in rCBF may ultimately permit correlational analysis of rCBF and behavior. Such an analysis may help to establish a link between behaviors and neurochemical changes that may provide clues to the pathophysiology of schizophrenia. Furthermore, changes in rCBF could potentially serve as a neurochemical target when screening novel antipsychotics for in vivo activity.

CONCLUSION

Neuroimaging has provided clinicians and researchers with an invaluable tool for the study of psychiatric disorders and their treatments. While the structural imaging techniques have been used widely to examine the neuropa-

thology of neuropsychiatric disorders, the functional and neurochemical techniques are only beginning to be used for this purpose. The examples of functional and neurochemical imaging discussed here illustrate the potential usefulness of neuroimaging for pathophysiologic studies and, more importantly, the drug development process. As these neuroimaging techniques become more advanced, it will become more desirable to use these direct, noninvasive methods to obtain information regarding drug effects in the brain.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others).

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