Applications of Positron Emission Tomography in Psychiatry

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Blood flow, metabolism, and structural imaging studies suggest altered neural circuits in major psychiatric disorders including mood disorders, schizophrenia, and obsessive compulsive disorder. Neuroreceptor mapping studies have identified serotonergic abnormalities in mood disorders and dopaminergic abnormalities in schizophrenia. Further imaging applications have involved development of new positron emission tomgraphy (PET) tracers that may identify abnormalities in peptide neurotransmitter systems such as corticotrophin releasing factor or substance P. Finally, PET can play an important role in quantifying the relationship between receptor occupancy, drug blood levels, oral dose and therapeutic outcome. In that way PET scanning can contribute to both therapeutics and to drug development by more rapid identification of the likely therapeutic dose range compared with conventional parallel group dose comparisons or dose ranging studies.

BRAIN IMAGING IS not yet part of clinical practice in psychiatry. Given that major psychiatric disorders involve altered brain biology, and the promising results emerging from research studies, one can predict that we are approaching the era where brain scanning will become part of psychiatric practice. It has potential for application in several areas of importance to psychiatry including diagnosis, biochemical sub-typing of major psychiatric disorders, selecting the treatment of first choice, monitoring treatment response and optimizing dose of medication, and in development of new psychotropic agents.

With regard to abnormal brain biology in psychiatric disorders, historically there was no way of directly demonstrating this, and indirect methods such as studies of cerebrospinal fluid metabolities of major monoamine neurotransmitters, measurements in peripheral blood, and neuroendocrine challenge tests, were the only indicators of abnormal brain function. Treatments that were beneficial for these disorders also implicated monoamine systems. More recently, elegant postmortem studies have identified abnormalities in major psychiatric disorders. For example, major depression is associated with widespread abnormalities in the serotonergic and noradrenergic systems.[1] Schizophrenia is associated with alteration in the dopaminergic system, such as up-regulated D2 dopamine receptors.[2,3]

The major imaging approaches that have been used in psychiatry are PET single photon emission computed tomography (SPECT) or magnetic resonance structural imaging, functional imaging mainly using the BOLD technique, and spectroscopy. Since SPECT has offered only blood flow studies and some receptor studies that are similar to the same work with PET, this paper will describe the imaging field illustrated by PET work only, in the interests of space and clarity.

GENERAL PET METHODS USED IN PSYCHIATRY

[^{18}F]-FDG

This approach allows measurement of glucose uptake. Most glucose metabolism in the brain is driven by the energy requirements of ion pumps and the glutamate-glutamine recycling system. Changes in regional brain glucose utilization are mostly due to differences in neuronal activity rather than to non-neuronal cells such as glia. Two main types of studies have been carried out. The first are studies of the brain at rest[4] or doing some basic task such as a neuropsychological attention task.[5] These studies have sought global or regional differences in brain activity. The second type of study was a challenge study, where the challenge could be pharmacological[6,7] affective,[8] or cognitive such as working memory.[9,10] Far more of these challenge studies have used blood flow as the outcome measure, but [^{18}F]-fluoro-2-deolyglucose (FDG) has the advantage that it is not confounded in the same way as blood flow measures by effects of pharmacological agents directly on cerebral circulation instead of indirect effects on blood flow due to changes in neuronal activity.

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0001-2998/03/3302-0005$30.00/0

doi:10.1053/snuc.2003.127302

Neuroimaging studies in mood disorders have generally reported functional deficits but disagreed about structural deficits.[11,12] For example, 11 of 12 studies of the prefrontal cortex (PFC) in depressed subjects found lower regional cerebral metabolic rate of glucose (rCMRglu),[12] compared with half or fewer studies reporting alterations in the volume of key brain regions hypothesized to play a role in mood disorders.[11] The ventromedial PFC with its limbic (anterior cingulate) and paralimbic (ventral PFC) components has been implicated in mood disorders.[11,12] Lesions involving the ventromedial PFC impair the experience of emotion and autonomic responses to emotional experiences.[13,14]

We found blunted relative prefrontal cortical (PFC) glucose uptake (rCMR glu) responses in several brain regions to the release of serotonin by fenfluramine in depressed subjects with mood disorders *in vivo* using PET and [^{18}F] (FDG).[15] Drevets et al[16] found a subgenual PFC region in subjects with familial mood disorders, exhibiting deficits of blood flow, metabolism, and smaller structural volume. Results of efforts to replicate his smaller subgenual gray matter volumetric finding have been inconsistent.[17,18] Mayberg et al[8] found higher blood flow and glucose metabolism occurred in ventral prefrontal regions, during induced sadness in controls, and an increase in flow and metabolism occurred with clinical recovery from depression in subjects. Reductions in frontal blood flow and glucose metabolism with treatment response in depression have been documented in other studies.[19,20]

We have tested brain response to serotonergic challenge by single-blind administration of an oral dose of placebo or of 60 mg (about 0.8 mg/kg) of dl- fenfluramine as described previously.[21,22] Fenfluramine raises intrasynaptic levels of serotonin both by release from nerve terminals and by inhibiting transmitter reuptake. We found a ventromedial PFC metabolic deficit on placebo in the depressed subject group compared with healthy volunteers. In this deficient area, glucose uptake suppressed further with serotonergic challenge. The results of our functional analyses are consistent with the finding of Drevets et al[16] of a region of lower rCMRglu in the subgenual cingulum in subjects with familial mood disorders. The brain region where we found a functional difference was slightly anterior and inferior to the subgenual region identified by Drevets et al,[16] although these regions overlap. The further decrease in metabolism we observed in the fenfluramine condition appeared to correlate with acute mood improvement. Mayberg et al,[8] assessed depressed subjects' metabolism before and after recovery from depression, but not relative to control subjects. Our study design involved a comparison with healthy subjects undergoing the same pharmacological challenge, demonstrating that relative regional metabolism was lower at baseline in depression and suppressed further with acute serotonergic challenge. If the acute metabolic response to serotonin elevation by fenfluramine is similar to metabolic change seen in recovery from depression, then our finding of a correlation with acute mood improvement suggests consistency between the prior results of Drevets et al[16] and of Mayberg et al.[8] The ventromedial PFC is hypoactive in depression and becomes more so with mood improvement. This apparently paradoxical suppression with recovery from depression has been found in both blood flow and metabolism in the frontal cortex in studies of antidepressant response to electroconvulsive therapy.[19,20] How this metabolic inhibition might contribute to mood improvement remains to be elucidated.

The absence of a difference in the magnitude of the fenfluramine challenge response between subjects and healthy subjects suggests normal serotonin function in this region. Alternatively, deficient metabolism, both pre- and post challenge, may involve a deficit of glial[23] or pyramidal cells that might interfere with glutamate transmission, the major mechanism of neuronal energy consumption.[24]

A number of studies in schizophrenia have found lower glucose uptake in prefrontal cortex in schizophrenia.[25,26] These results are consistent with blood flow studies[9,27] and with impaired blood flow responses during a working memory task, where performance in schizophrenia has been shown to be impaired.[9]

Obsessive compulsive disorder is associated with higher thalamic blood flow and elevated glucose utilization in basal ganglia but lower in ventral prefrontal cortex.[28] Interestingly, a favorable clinical response to either medication or psychotherapy, results in a diminution of the hypermetabolic activity.[29]

[^{15}O]-Water

[^{15}O]-Water affords a useful way of studying regional brain differences in cerebral blood flow. Because ^{15}O has a half-life of about two minutes,

it is possible to give an injection every 12-15 minutes, and get a new snapshot of blood flow. Acquisition begins as soon as the tracer leaves the large cerebral vessels to enter the smaller vessels in the brain that permeate the brain parenchyma. Acquisition time is usually 60-90 seconds. Such blood flow studies are complemented by SPECT studies using mostly HMPAO. Results of blood flow studies in depression tend to indicate a prefrontal cortical deficit.[30,31]

In schizophrenia, the results also favor an anterior deficit, and in particular deficits in responses to the Stroop and other tasks of working memory.[9,32]

Neuroreceptor Mapping

The Serotonin System in Mood Disorders

Abnormal serotonin (5-HT) transmission is implicated in major depression.[33,34] The serotonin transporter, located on the serotonin presynaptic nerve terminals, terminates the action of intra-synaptic 5-HT by reuptake.[35] Serotonin transporter binding is a marker of serotonergic innervation,[36] and the level of intra-synaptic serotonin, which regulates transporter internalization. For example, internalization is decreased in the presence of lower synaptic levels of serotonin.[37] Therefore less transporter binding indicates fewer serotonin nerve terminals or less intra-synaptic serotonin, and the effect of either state is likely to represent less serotonin function. We found less postmortem serotonin transporter binding throughout the dorsal-ventral extent of the prefrontal cortex[38] and in the brainstem[39] of individuals with a history of an episode of major depression. *In vivo* imaging studies of the serotonin transporter in major depression have reported conflicting results.[40-44] SPECT studies of the serotonin transporter with [^{123}I]β-CIT have limitations of resolution and can reliably quantify SERT binding only in the brainstem. Positron Emission Tomography (PET), using a tracer such as [^{11}C]McN5652 or [^{11}C]-DASB, can quantify serotonin transporter binding *in vivo* in multiple brain regions.

We have found lower transporter binding using PET and [^{11}C]McN5652 in several brain regions associated with the limbic-striatal-pallidal-thalamic-cortical circuit, implicated in mood disorders by imaging studies of blood flow and glucose metabolism (for review see Soares and Mann[12]). We found that the midbrain, amygdala, and ventral striatum have lower binding in depressed subjects. In contrast, the thalamus seems to be spared. The signal to noise ratio with the PET ligand, [^{11}C]-McN 5652, does not permit reliable measurement of binding in prefrontal cortex. Nevertheless, it appears that the changes in SERT binding in major depression are region specific, widespread but not global. That observation further supports the notion of a specific circuit underlying the pathobiology of mood disorders and tends to rule out non-specific global effects on tracer kinetics.

The amygdala encodes affectively laden memories.[45] A mood challenge involving induction of depressed mood alters blood flow in the amygdala[46] although, there is disagreement regarding structural and functional abnormalities in the amygdala in mood disorders.[11,12,47,49] Drevets et al[50,51] reported higher flow and metabolism in the amygdala and thalamus but lower in the striatum. In contrast, we find low or normal serotonin transporter binding in all three structures. Therefore, the direction of change in transporter binding differs from that of metabolism and blood flow reported in mood disorders, indicating the importance of neurotransmitter imaging studies to complement mapping studies that use flow and metabolism.

Lower serotonin transporter binding in mood disorders could be due to a functional change in the distribution of transporters or due to fewer transporters. Lower intra-synaptic serotonin due to any cause such as a deficiency of serotonin for release can result in accelerated serotonin tranpsorter internalization,[37] an effect that would reduce serotonin re-uptake and raise intra-synaptic levels, thereby compensating for less serotonin release. Alternatively, there may be fewer serotonin nerve terminals due to fewer serotonin neurons or fewer or dysfunctional neuronal processes. The number of serotonin neurons is not lower in depressed suicides studied postmortem,[52] suggesting there may be fewer terminals or fewer transporters per terminal. This latter hypothesis is supported by a report from Austin et al[53] who found fewer serotonin processes postmortem in the prefrontal cortex of depressed suicides. We have found in depressed suicides postmortem, a lower density of neurons in ventral prefrontal cortex in association with fewer transporter sites overall, but not per cortical neuron.[52] Therefore, less serotonin transporter binding appears to be the result of fewer serotonin terminals.

Major depression, particularly when severe and

requiring hospitalization, is associated with elevated levels of cortisol, due to a combination of factors including adrenal cortical hypertrophy and failure of cortisol feedback inhibition via corticosteroid receptors in the hippocampus and perhaps hypothalamus. Exposure to stress is reported to cause neuronal damage via hypercortisolism, most notably in the hippocampus,[58,59] and that hippocampal damage may, therefore, contribute to and result from a major depressive episode. Lifetime days in a major depressive episode are inversely correlated with hippocampal volume.[47] Corticosteroids or exposure to chronic unpredictable stress in rats reduces 5-HT_{1A} mRNA,[60] and 5-HT_{1A} receptor number, in the hippocampus.[61] Less hippocampal 5-HT_{1A} binding and mRNA has been found in depressed suicide victims.[60] Data from neuroendocrine studies indicate 5-HT_{1A} receptor blunted responses in the pathophysiology of major depression.[54-57]

[^{11}C]-WAY-100635 is a PET ligand for 5-HT_{1A} receptors in nonhuman primates and humans[62-64] and lower binding has been reported in depressed subjects compared with healthy volunteers.[65,66] We conducted a PET study using [11C]-WAY-100635 in major depression and found lower hippocampal and midbrain 5-HT_{1A} binding in depressed subjects compared with healthy volunteers. The hippocampal findings are consistent with a corticosteroid effect, although that remains to be demonstrated in man. We also found lower binding in depressed subjects in the anterior cingulate cortex, and that depressed females showed bigger differences than depressed males.

The Dopamine System in Schizophrenia

Antipsychotic medications share a common property of dopamine D2 receptor antagonism. This has been a major reason for the dopamine hypothesis of schizophrenia. Direct evidence has been lacking for this hypothesis. PET studies of D2 receptors using [^{11}C]-raclopride have tended to find no differences in unmedicated[67] or medication naive schizophrenics, but [^{11}C]-N-methyl-spiperone studies[68] have tended to find more D2 binding. The question of alternation in D2 receptor binding in schizophrenia remains unresolved but presumably has something to do with the differences in the ligands or in the study populations. Another strategy for imaging the dopamine system is to manipulate levels of dopamine and measure those changes using a PET ligand sensitive to the effects of competition of the intra-synaptic dopmine level for binding to the D2 receptor. [^{11}C]-raclopride is such a ligand, and release of dopamine by amphetamine results in less [^{11}C]-raclopride binding to the D2 receptor. That decrease in [^{11}C]-raclopride binding, quantified in the striatum using a PET scanner, has been shown to be proportional to the amount of dopamine released.[69] In unmedicated schizophrenia, the dopamine release after amphetamine is higher as measured by PET scanning and the decrease in [^{11}C]-raclopride in the striatum,[69] and represents important evidence that the dopamine system may be overactive at least at the level of the striatum.

PET in Psychotropic Drug Development

[^{11}C]-raclopride has been used to show that typical or classical antipsychotics such as haloperidol tend to block over 70-80% of D2 receptors in the striatum at doses that have a therapeutic effect,[70] whereas atypical or newer generation antipsychotics, tend to block fewer than 70% of D2 receptors at therapeutic doses. That may explain why atypical antipsychotics produce few or no extra-pyramidal side effects.

Antidepressants that enhance serotonin function by reuptake inhibition, such as the SSRIs, have a therapeutic effect that evolves over weeks. To explain why these medications do not work more rapidly, it has been thought that the rapid, initial rise in serotonin, inhibits firing of serotonin neurons through 5-HT_{1A} auto-receptors located on the serotonin cell bodies and proximal dendrites. Animal studies indicate that these 5-HT_{1A} auto-receptors desensitize progressively over weeks and the consequence is an increase in the firing rate of serotonin neurons. The greater release of serotonin due the higher firing rate is thought to result in higher serotonin levels at the post-synaptic receptors and an antidepressant effect. Pindolol, best known as a beta blocker, is also a 5-HT_{1A} antagonist. PET studies using [^{11}C]-WAY-100635 have shown that pindolol binds with higher affinity to brainstem 5-HT_{1A} autoreceptors than to postsynaptic receptors. Thus, by blocking the autoreceptor, pindolol has the potential of accelerating or augmenting the antidepressant effects of antidepressant medications such as the selective serotonin reuptake inhibitors (SSRIs). It has not been clear why the controlled clinical trials of pindolol aug-

mentation have produced discrepant results. PET studies using [^{11}C]-WAY-100635 have provided an explanation[71-74] by showing that the dose of pindolol used in most of the controlled studies was too low to adequately block the 5-HT$_{1A}$ autoreceptor.

Another set of studies have examined the degree of serotonin transporter blockade produced by SSRIs in the doses commonly used to treat depression,[43] and found that the lower doses usually used will block over 80% of transporter sites. Therefore, benefit found with high doses, are likely to be due to other effects. Some SSRIs have other pharmacological effects at higher doses including on the norepinephrine transporter.[75] An exception would be individuals who metabolize the drug very rapidly relative to the general population. Nevertheless, PET studies are able to provide precise information about general therapeutic dose ranges when a tracer is available for the site of therapeutic action. Such information can accelerate drug development and improve clinical practice.

SUMMARY

Several promising imaging findings in psychiatric disorders provide some of the best and most direct evidence obtained to date that there are abnormalities in major neurotransmitter systems in serious psychiatric disorders. These advances are the initial steps in the process of making clinical use of imaging methods such as PET part of psychiatric practice. In addition, important applications for PET exist in drug development.

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