January 1994

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Recommended Citation

Kapur, MD, Shitij; Houle, MD, PhD, FRCP (C), Sylvain; and Brown, MD, PhD, FRCP (C), Gregory M. (1994) "Positron Emission Tomography in Psychiatry: New Sights, New Insights," *Jefferson Journal of Psychiatry*. Vol. 12 : Iss. 1 , Article 10.

DOI: <https://doi.org/10.29046/JJP.012.1.007>

Available at: <https://jdc.jefferson.edu/jeffjpsychiatry/vol12/iss1/10>

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Positron Emission Tomography In Psychiatry: New Sights, New Insights

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Abstract

Positron Emission Tomography (PET) is a new tool with which to explore the neurobiological basis of psychiatric illness. PET permits in-vivo measurement of regional cerebral blood flow, regional glucose metabolism, as well as information about neurochemicals and their receptors. Since regional cerebral blood flow and glucose metabolism reflect ongoing neuronal activity, the neural bases of different cognitive processes and emotional states can be discerned using PET. Findings from recent studies in schizophrenia, affective disorders, obsessive-compulsive disorders, anxiety disorders, and dementia are reviewed with a special emphasis on how these findings may be useful in developing a more comprehensive framework for understanding the neurobiological basis of psychiatric disorders. The relationship between PET and other brain imaging modalities, the imminent improvements in PET technology, as well as future directions of research are discussed.

INTRODUCTION

Neurobiological factors are important determinants of psychiatric illness. However, how these neurobiological factors lead to the observed psychiatric symptoms is far from clear. Investigations using indirect (e.g. plasma, urine and cerebrospinal fluid neurochemistry, receptor expression in peripheral sites) and direct indices (e.g. CT scans, MRI scans, surface electrophysiological recordings, neuroendocrine challenges) have confirmed the association between neurobiological factors and psychiatric illnesses. However, in the absence of a comprehensive framework for understanding behavior and emotion in the context of brain function, these findings remain isolated empirical facts. The challenge now is to unite these facts into a useful theoretical framework—one which will permit a pathophysiological understanding of psychiatric illness, and a rational basis for the treatment of these disorders. Herein lies the promise of PET.

PET offers the opportunity to develop a unified theory relating emotions and behavior to neurophysiological and neurochemical events in a neuroanatomical

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context. To illustrate, it is known that certain focal lesions (e.g. left frontal strokes), or certain systemic neurochemical alterations (e.g. sympathomimetic withdrawal), or profound psychosocial stress (e.g. death of a spouse) may all lead to a depressive syndrome. Furthermore, all the above cases may respond to treatment with a serotonin-specific reuptake inhibitor (SSRI) antidepressant. PET offers, at least in principle, the opportunity to unify these isolated facts. By elucidating the network of brain regions subserving mood (1), it may help us to understand why left frontal strokes are particularly crucial in inducing depressive symptoms. By specifying how cognition and stress influence this network of regions, one may understand how situational factors may induce depression. By unraveling the role of neurotransmitters in the modulation of this 'mood network', one may understand how sympathomimetic withdrawal induces depression and SSRIs treat it (2).

In this article, we review PET as it is relevant to the field of psychiatry. The first section will provide the readers with a glimpse into the physical principles and the instrumentation as relevant for the interpretation of PET studies. The second section will describe the physiological parameters that can be measured using PET. The third section reviews how PET studies have contributed to our understanding of various psychiatric illnesses. Finally, we outline the relationship of PET to other imaging modalities and the future technical and experimental improvements which may be important from the perspective of psychiatry.

HOW IS PET SCANNING DONE?

PET scanning depends upon the visualization of radiolabelled tracers introduced into the body. There are two major components to a PET program—radiochemistry and imaging. The account below is intentionally brief—for a more thorough account the reader is referred to more comprehensive sources (3–5).

Radiochemistry

The tracers used for PET are specially synthesized molecules which contain a positron-emitting isotope. Positron-emitting isotopes of common elements like carbon, oxygen, nitrogen and fluoride (C, O, N and F respectively) are preferred since these elements naturally occur in a wide variety of biologically relevant molecules. These isotopes have short half-lives (^{11}C —20 minutes, ^{15}O —2 minutes, ^{18}F —110 minutes) which necessitates a cyclotron facility, which generates the isotopes, either on-site or near the scanning facility. Once the isotope is produced, it is incorporated into the molecule of interest (e.g. ^{15}O is incorporated in water for blood flow studies, and may also be inhaled in a gaseous form; ^{18}F is attached to deoxyglucose for glucose metabolism studies; ^{11}C is incorporated into raclopride, resulting in ^{11}C -raclopride, which binds to dopamine D_2 receptors). This process of incorporating the isotope into the tracer agent is particularly demanding since high levels of chemical purity and specific-activity have to be assured in a short period of time as the isotopes are rapidly decaying.

Imaging

The scanning is done with the subject lying horizontally. The tracer is administered via an injection or, if gaseous, via inhalation. The amount of radioactivity administered, the time of administration, and the duration of uptake all vary depending upon the exact nature of the tracer and the purpose of the study. As the tracer undergoes rapid decay it emits positrons. The positron, a positively charged particle, travels a short distance (less than 3 mm) in the tissue and then combines with an electron. This combination leads to the generation of two 511 keV photons which travel in diametrically opposite directions. The ring of high-sensitivity detectors surrounding the head (the camera) detects these photons. As the two photons emitted from a single positron-electron combination, traveling in diametrically opposite directions, strike two diametrically opposite detectors, a 'coincidence event' is recorded. The coincidence event is the building block of the PET image. Thousands of such coincidence events are recorded during each scan and are used to reconstruct the image of the tracer distribution in the head. This reconstructed image constitutes the PET scan. With knowledge of the amount of tracer injected, and its distribution within the different body compartments, the acquired image can be converted into quantitative physiological data. For example, a PET image obtained with fluorodeoxyglucose as a tracer can be converted into a metabolic image which estimates regional brain metabolism in terms of milligrams of glucose metabolized per 100 gm of tissue per minute in different parts of the brain. Thus, PET not only images the functioning of the brain, it also measures it (6).

WHAT CAN BE MEASURED WITH PET?

Studies done with PET in the last decade can be broadly divided into three types: cerebral blood flow studies; glucose metabolism studies and neurochemical studies.

Cerebral Blood Flow (rCBF) Studies

The tracer used for rCBF imaging is usually water containing ^{15}O , injected intravenously. The scanning begins immediately after the injection and lasts 60–120 seconds. ^{15}O has a short half-life and the tracer decays almost completely within 10 minutes of injection. This allows the procedure to be repeated up to 12 times in a single session (7). rCBF closely reflects regional neuronal activity (8), and hence, by repeating scans while the subject is engaged in different tasks, and by comparing the brain regions activated in the different tasks, one can discern the brain regions involved in specific cognitive operations (9–11). In a prototypical application of this strategy, Petersen and colleagues (10) scanned subjects during three different cognitive tasks—passive viewing of presented words, oral repetition of presented words, and generation of verbs associated with the presented words. By comparing the rCBF scans obtained during the different tasks they were able to delineate areas

of the brain which were involved in the visual recognition of words, in the production of speech, and in the act of semantic association (10).

Cerebral Glucose Metabolism (rCMGlu) Studies

The tracer, ^{18}F -fluoro-deoxyglucose (FDG), is taken up by the tissues in a manner similar to naturally occurring glucose, but once inside the cell, FDG does not undergo further metabolism and is trapped (12). The tracer is injected intravenously, and is taken up by the brain over the next 45–60 minutes. Tracer 'uptake' is proportional to the rate of glucose metabolism in a given region and reaches equilibrium in 45–60 minutes. Once equilibrium is reached the scanning begins and may require 15 to 30 minutes to acquire a high-resolution image (12). An important difference between a rCBF and a rCMGlu PET scan is that the former reflects brain activity over 60–90 seconds whereas the latter reflects activity over 45–60 minutes. In addition, ^{18}F has a much longer half-life, and therefore the FDG scans cannot be repeated within a single session. Since ^{15}O -water scans reflect brain activity over briefer epochs and can be repeated multiple times within a session, these scans are the preferred measure for comparing neural activity in different cognitive, emotional or sensori-motor tasks (13).

Neurochemical Studies

These studies use specific ligands to determine the concentration and distribution of receptors, neurotransmitters, and other neurochemicals within the brain (14,15). For example, raclopride, an antipsychotic which binds to the dopamine D_2 receptor is frequently used. ^{11}C labeled raclopride can be used to visualize the level of D_2 dopamine receptors in the human striatum, and to compare the level of these receptors in the striatum of patients with schizophrenia to those of normal controls (16–18). These studies involve the synthesis of a positron-emitter (^{11}C or ^{18}F or ^{76}Br), incorporation of the isotope into the tracer molecule, injection of the tracer, PET scanning, and finally, application of mathematical models to convert the image into quantitative estimates of the concentration of the receptor or neurochemical (19,20). As newer ligands are being synthesized more and more receptors and neurotransmitters are becoming accessible to *in-vivo* measurement (21).

SAFETY

The radiation exposure from a PET scan is comparable that of other diagnostic procedures used in nuclear medicine, and therefore is easily defensible in patients who are receiving direct benefit from the investigation. The issue is more complex when these techniques are used in normal volunteers or in research studies where there is no direct benefit to the patient. The radiation exposure from a PET scan is determined by the nature of the tracer, the amount of radioactive material administered, route of administration, and the total number of scans. As a broad generaliza-

tion, the exposure may vary from a fifth to nearly double of what the normal population receives from background radiation sources within a year. In keeping with this, most research centers limit the number of times a normal volunteer can participate in PET experiments and the number of scans a volunteer can undergo in a single study.

PET STUDIES OF RELEVANCE TO CLINICAL PSYCHIATRY

Schizophrenia

The most enduring PET finding in schizophrenia is that of frontal dysfunction—the pioneering studies by Buchsbaum et al. reported “frontal hypometabolism” (22–25); a finding which has since been observed by most (26–28), though not all groups (29,30). Cleghorn et al. (31), on the other hand, report a relative frontal hyper-metabolism. PET scans of patients have been compared to controls while both were undertaking a smooth-pursuit eye-tracking task (32,33), and while performing tasks requiring sustained attention (25,34,35); both representing tasks on which patients with schizophrenia typically show impaired performance. Task-based comparisons accentuate the resting-state differences between normals and patients in the frontal lobes (25,32–35) suggesting that not only is there a frontal dysfunction at rest, but that the response of the frontal lobe to the task demands is also deficient in patients with schizophrenia (36–38). In addition to investigations of the frontal lobe, the role of the temporal lobe (24,39–41), parietal lobe (40,42), and hemispheric asymmetry have been evaluated using PET (43,44) though the PET evidence for impairment in these regions is less convergent (45).

Studies have sought to correlate clinical symptoms to regional brain abnormalities (27,46). It appears that the onset of symptoms may be associated with frontal hyper-function (31), while with chronicity of symptoms and neuroleptic treatment the picture may change to one of frontal hypometabolism (27,31,32). Cleghorn and colleagues (47) compared patients who were actively hallucinating to those who were not and found that patients with active hallucinations had significantly lower metabolism in the auditory and Wernicke’s area and a higher metabolism in Broca’s area. Liddle and colleagues (48,49) report a correlation between psychomotor poverty and left dorso-lateral prefrontal cortex abnormalities, conceptual disorganization and anterior cingulate region abnormalities, and hallucinations and delusions and medial temporal cortex abnormality. Relating phenomenology to abnormalities in discrete brain systems raises the possibility of a brain-based understanding of the different syndromes and sub-syndromes of this complex illness.

The dopamine hypothesis of schizophrenia is one of the most enduring neurochemical hypotheses of schizophrenia. However, dopamine receptor studies using PET have yielded conflicting findings (50). Wong and colleagues (51–53) reported a 2.5-fold increase in the dopamine D₂ receptors in the caudate-putamen of patients with schizophrenia using ¹¹C-N-methylspiperone as a ligand. In contrast, Farde (54,55) and Heitalla (18) using ¹¹C-raclopride as a ligand, and Martinot (56) using

⁷⁶Br-bromolisuride, failed to find this increase. Differences in patient selection, differences in ligand characteristics, and differences in the mathematical modeling of the data have been suggested as possible causes for the observed differences in results (57). Studies with newer ligands will be required before the issue of D₂ dopamine receptors in schizophrenia is conclusively resolved (52,55,58).

There is greater convergence, on the other hand, among studies investigating the relationship between D₂ receptor binding and neuroleptic treatment. The percent occupancy of the dopamine receptors in the striatum is closely related to plasma neuroleptic levels, though changes in receptor occupancy lag behind the changes in plasma levels (59–61). At the usual clinical dose, typical neuroleptics occupy 70%–85% of the available D₂ receptors, an effect that is achieved, in most cases, at doses equivalent to about 150 mg of chlorpromazine (62–66). The atypical neuroleptic clozapine, on the other hand, shows a lower occupancy of D₂ receptors (30–50%) and a higher occupancy of D₁ and possibly S₂ receptors (62–67). Receptor occupancy, beyond a certain threshold, does not seem to increase therapeutic effects but does tend to increase the level of extrapyramidal side-effects (68–71). Taken together the evidence suggests that with typical neuroleptics, a certain level of D₂ receptor occupancy (70% or greater) is necessary, but may not be sufficient for a therapeutic effect. In addition to blocking the receptors, neuroleptics increase metabolism in the caudate-putamen (30,40,72–75). At present the relevance of this finding is not clear. However, as the role of the striatum in cognition is unraveled further, it may become possible to understand the mechanism of neuroleptic medications in terms of their neuromodulatory effect on the striatum (75).

These initial studies in schizophrenia have offered promising leads. First, there is strong evidence for frontal dysfunction in schizophrenia, both at rest and while engaged in specific tasks; other cortical and subcortical regions may also be involved. Second, groups of symptoms can be related to a dysfunction of specific brain regions. Third, neuroleptic drugs produce significant changes in brain metabolism in the striatum via the occupancy of dopamine receptors. Fourth, a high level of dopamine D₂ receptor occupancy is necessary for clinical response, but is not sufficient by itself. Fifth, the differences in the clinical profile of typical versus atypical neuroleptics may be related to the differences in the occupancy of the D₂ and D₁ and possibly S₂ receptors. These findings are preliminary, but they offer the hope of developing a comprehensive understanding of the pathophysiology of schizophrenia and a rational approach to its treatment.

Affective Disorders

PET has made possible the study of the neuroanatomical pathways modulating mood. Pardo and colleagues have reported the involvement of the inferior frontal cortex in self-induced dysphoria in normal subjects (1). In patients, depressive symptoms are associated with a hypo-perfusion and hypo-metabolism in the prefrontal cortex (6,76–80). It is unclear if this defect is similar to that seen in schizophrenia (81); it has recently been suggested that prefrontal hypo-metabolism may reflect

psychomotor poverty, and that this may be the reason for prefrontal hypo-metabolism being observed in both schizophrenia and depression (82). Prefrontal cortex hypo-metabolism seems to be correlated with symptom severity and a resolution of clinical symptoms is accompanied with a trend towards normalization of this defect (78,83,84). In addition to the frontal hypo-metabolism, studies have reported an involvement of the caudate-putamen (85) as well as limbic structures in depression (6,80).

Previous studies investigating the neurochemical changes accompanying depression had to infer changes in the brain via peripheral measures such as receptors on peripheral cells or the neurotransmitter metabolites measured in the cerebrospinal fluid, plasma and urine. PET makes possible direct, *in-vivo* measures. Kishimoto and colleagues (86), using radiolabelled amino acids, reported a significant decrease in the amino acid pool in patients with depression and a significant increase in patients with mania. Agren and colleagues (87) reported a decreased transportation of ^{11}C -L-5-hydroxytryptophan across the blood-brain barrier in patients with depression. Using ^{11}C -N-methylspiperone (^{11}C -NMSP); a ligand which binds to the dopamine D_2 and serotonin S_2 receptors (88), Mayberg and colleagues (89) report that after unilateral strokes, ^{11}C -NMSP binding negatively correlated with the degree of depressive symptoms. This suggests that a decrease in serotonin S_2 receptor number or an inability to up-regulate S_2 receptors in the ipsilateral hemisphere after a stroke may be associated with the symptoms of depression.

Thus, metabolic PET studies in depression implicate the prefrontal cortex, the caudate-putamen, and limbic structures as candidate structures subserving mood (1,6,80). These findings help explain, at least in part, the increased propensity for developing depression secondary to stroke involving the frontal cortex, Parkinson's disease and Huntington's disease. The neurochemical and neuroreceptor studies using PET in depression have demonstrated the potential of *in-vivo* study, but there are few convergent or replicated findings. What is needed now are systematic studies which on the one hand identify the neuronal and neurochemical correlates of depressive symptoms, and on the other hand delineate the neurochemical effects of antidepressants which are crucial for the resolution of mood symptoms.

Obsessive Compulsive Disorder (OCD)

In a series of pioneering studies Baxter and colleagues described an elevation of metabolism in the right orbital gyrus and the caudate nucleus in OCD (90,91). Subsequent studies by Baxter and colleagues and by other groups with more carefully selected drug-free non-depressed OCD patients confirmed this finding (90-93). Clinical improvement, whether due to pharmacological treatment (fluoxetine and clomipramine) or behavior therapy is associated with a normalization of the striatal hyper-metabolism (93-95).

These findings suggest that symptoms in OCD result from the generation of self-sustaining, improperly inhibited, positive feedback loops of motor and cognitive activity in frontal-striatal/limbic-thalamic circuits (96). In a symptom induction

study, Rauch and colleagues (97) scanned patients with OCD while in an asymptomatic state and subsequently while experiencing experimentally-induced obsessive-compulsive symptoms. The symptoms were associated with an increased rCBF in the frontal-striatal-limbic circuit providing support for the above described model (97). It is remarkable that with the advent of functional imaging, in-vivo evidence is now available to identify a neurobiological basis for an illness which until recently was considered a prototypical 'functional neurosis'. This does not suggest that psychodynamic principles are superfluous, but it does suggest that the dichotomy between functional and organic illnesses may no longer be tenable. In fact, psychodynamic and biological explanations may be two complimentary levels of abstraction with which to understand the symptoms of OCD. Each framework may offer unique insights and unique treatments.

Anxiety Disorders

Anxiety disorders are the most common of psychiatric disorders, and yet little is known about the neuroanatomical basis of anxiety (98). Initial PET studies of patients with panic disorder suggested that at least a subset of them showed metabolic asymmetry in the hippocampal region (99). To test this hypothesis, Reiman and colleagues (100–102) induced panic attacks in susceptible subjects during the PET scan itself and found significant increases in the rCBF in the temporal poles, insular cortex, claustrum and putamen. However, these findings have subsequently been questioned and other groups fail to find the same results (103).

Dementias

Although no pathognomonic pattern of brain dysfunction diagnostic of dementia has emerged, patients with Alzheimer's disease do show a relative reduction in metabolism in the frontal and temporo-parietal association areas when compared to age-matched controls. There also seems to be an inverse correlation between overall symptoms and regional metabolism (104). In addition, there seems to be a significant loss in the serotonergic receptors in frontal and temporo-parietal cortical regions (105). The effects of the dementing illness are hard to distinguish since they are confounded by the effects of normal aging on metabolism (106,107), receptors (88), and structural atrophy. While at this time the clinical utility is limited, it is hoped that with the application of advanced statistical methods (108) and cognitive-challenge techniques (109) PET could play an important role in the early diagnosis of dementia (108,110), in differentiating Alzheimer's disease from multi-infarct dementia (111–113), and in distinguishing dementia from depression (114) and other confounding illnesses (111).

PET AND OTHER IMAGING MODALITIES

PET provides the information about brain function. CT and the MRI techniques, on the other hand, provide the neuroanatomical information. The techniques complement each other, and by co-registering a MRI scan of a given individual to their PET scan the anatomical precision of the interpretations of the PET data may be improved (115). Recently, MRI scanners have been used to obtain information about regional changes in hemoglobin saturation; a technique which provides information similar to that obtained from PET rCBF studies (116–118). This technique of “functional MRI” is new, but once standardized, offers the potential of providing information regarding rCBF with greater anatomical precision and no radiation risk. Nuclear magnetic resonance spectroscopy uses magnetic resonance for measuring the level of neurochemical metabolites in different regions of the brain (119). The metabolites measured are different from those assessed using PET and therefore the two techniques can complement each other.

Single photon emission computed tomography or SPECT is an imaging modality which is functionally similar to PET. The major difference between the two is the nature of the tracer and the degree of spatial resolution. Tracers used in PET imaging involve short-lived isotopes of C, N, O and F. While this permits the production of a wide variety of biological agents, it necessitates a cyclotron for the production of the tracers. SPECT imaging, on the other hand, incorporates long-lived isotopes of technetium and iodine. Since these elements do not naturally occur in a wide variety of biological chemicals, it limits the variety of compounds which can be produced, but since the half-life of the tracers is long, the tracers can be produced at a remote site and shipped to the camera-site for imaging. The present generation of PET cameras provide a higher degree of spatial resolution; however, with increasing sophistication in SPECT technology this difference in resolution is narrowing. Thus, PET imaging, due to the wider range of available ligands and higher resolution, may be more useful as a research tool in the initial stages of investigation. SPECT, due to its lower cost and greater availability, would be the vehicle for the wider dissemination of the useful research and clinical applications derived from initial PET studies.

PET AND PSYCHIATRY-WHAT DOES THE FUTURE HOLD?

The PET technology is undergoing continuous improvement; the in-plane resolution has reached the theoretical maximum of about 3 mm. (3,5). PET and MRI images can be co-registered using automated software (120–122). Automated methods are now becoming available for image analysis (123–125). In addition, new statistical methods are being developed which will permit the comparison of brain networks rather than single regions (126–130).

It is now well recognized that dynamic tests, such as the cardiac stress test and the glucose tolerance test, are more sensitive and specific measures of the functional status of the respective physiological systems than baseline measures. Such ap-

proaches should now be implemented in the field of psychiatry using PET. For example, rather than comparing schizophrenic patients with controls at rest, patients should be studied while engaged in cognitive tasks which best differentiate them behaviorally from their controls. Thereby, one would not only identify brain abnormalities, but more usefully, understand brain abnormalities which are specifically related to the functional deficits shown by the patients (36,38). Mood states and anxiety levels can be modified experimentally in safe and ethical paradigms. Standardized "emotional challenges" should be developed and used with PET to delineate the neural networks which subserve mood (1,2,97,102,103). Moreover, PET permits the *in vivo* study of the interaction of pharmacological, cognitive, and emotional states (131,132). These approaches could be combined and the behavioral effects of drugs could be understood in terms of their neuroanatomically specific modulation of networks. Such studies may permit us to develop a comprehensive neurobiological framework of human emotion and behavior as a basis for understanding psychiatric illness (2).

The findings which will emerge using these new techniques and paradigms, in all likelihood, will not accommodate themselves in our present conceptual niches. Diagnostic systems, our ability to classify and categorize observable phenomenon, are the bedrock of scientific research and serve the purpose of identifying a relatively homogenous group of patients who can then be studied and with respect to whom predictions can be made. As opposed to the rest of modern medicine where nosology is primarily pathophysiology-based, the present system of classification in psychiatry is based on the identification of a cluster of symptoms. While such diagnostic systems have and may continue to serve us well clinically, this may not be the best way to identify homogenous groups of patients for neurobiological research. The real challenge then, will be to go beyond our current diagnostic constraints and look at the symptoms that cut across syndromes and syndromes that cut across disorders (82). For example, the same brain systems may subserve psychomotor poverty, irrespective of whether they are encountered in depression or schizophrenia. On the other hand, different brain systems may subserve psychomotor poverty and delusions/hallucinations even though these symptoms are clustered together under the diagnosis of schizophrenia (82). Thus, brain-based physiological systems, in addition to phenomenological clustering, may become the basis for diagnosing and treating psychiatric illness (2,36,133). PET has opened the window to the brain—the next decade will determine if it will change our vision of mental illness.

ACKNOWLEDGMENTS

Dr. Shitij Kapur was supported by a Research Fellowship from the Ontario Mental Health Foundation. The authors would like to thank Dr. Robert Zipursky and Dr. Craig Hudson and Randi Rose for their constructive comments on this manuscript.

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