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EDITORIAL

PET Studies in Psychiatry: Validity, Accuracy and Future

PET with its high resolution and array of ligands again demonstrates its vitality and power in the series of preceding papers which illustrate its reproducibility, clinical utility and value in understanding metabolic function.

Degeneration of nigral dopaminergic neurons of the caudate nucleus, putamen and globus pallidus underlies the pathogenesis of Parkinson's disease with its characteristic movement disorders. Fluorine-18-L-6-fluorodopa (FD) is a substrate for the enzymes involved in L-dopa metabolism. FD is converted to fluorodopamine. In normal subjects, FD accumulates within the striatum. In patients with Parkinson's disease, striatal uptake is reduced. As an important index of nigro-striatal dopaminergic function, FD uptake has been used in studies of schizophrenia, Parkinson's disease and intracerebral transplantation of adrenal and fetal tissue.

Dr. Vingerhoets and coworkers (*1*) address an important issue of intra-subject and intersubject variations in striatal uptake of FD. They observed that FD-PET yields reproducible results with reliability coefficients between 73%–90%. They made an important and significant observation that variation in blood radioactivity contributed to the variability of Ki more than metabolite correction. However, separation of FD from its metabolites is essential for each FD-PET scan. This study demonstrates that PET measurements in normal subjects are stable across repeated scans, a finding indicative of wide normal variation in dopaminergic function which lends credence to recent risk studies.

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Sawle et al. (*2*) reported that they have been able to identify presymptomatic Parkinson's disease patients in a large Irish family using FD scans and putamen assessment. Burns et al. (*3*) found decreased FD uptake in asymptomatic co-twins of patients; this is also consistent with the use of PET scans as an index of risk. Although risk studies of this kind have not yet been carried out in large populations, the implications for early treatment cannot be ignored. Parallel studies with FDG would allow us to answer important questions about the relationship of striatal dopamine change to changes in striatal projection areas and cortical regions involved in dementia.

Alzheimer's disease is characterized clinically by impaired memory, cognitive and behavioral function. CT and MRI of Alzheimer's disease brains shows ventricular dilation and cortical atrophy with the widening of sulci. Histopathological studies show neural degeneration with neurofibrillary tangles, senile plaques, cerebral amyloid, as well as neuronal perikaryal losses in the nucleus basalis of Meynert, the hippocampus, amygdala and cerebral cortex.

In the last 10 yr, PET studies have focused on evaluating specific changes in glucose metabolism using FDG. Decreased glucose metabolic rates in temporoparietal and frontal regions with relatively well preserved metabolism in primary visual and sensorimotor areas, and in the basal ganglia and cerebellum have been reported in the early stages of Alzheimer's disease. It has been more difficult to relate parietal changes to the early symptoms of memory loss.

In this issue of the *Journal*, Dr. Kippenhan and coworkers (*4*) in Miami and Bethesda demonstrate the power of FDG-PET and neural-network classification to discriminate patients with probable Alzheimer's disease from normal controls. Quantitative computer algorithms are harnessed in an impressive analysis with 90% sensitivity. They demonstrate improved patient identification with greater scanner resolution (FWHM) in an interesting comparison between the PETT V scanner (15 × 15 × 15 mm) and a Scanditronix PC1024-7B scanner (6 × 6 × 10 mm). Recently, Herholz et al. (*5*) compared FDG-PET studies in probable Alzheimer's disease among three European centers with different PET scanners (in-plane resolution ranging between 6.75 and 9.2 mm). Using a composite ratio (glucose metabolism in the most typically affected region over the least typically affected region), they reported a diagnostic accuracy of 95.8%. These studies clearly demonstrate that increased resolution of PET scanners improves diagnostic accuracy of early Alzheimer's disease.

Fazekas et al. (*6*) have suggested that glucose metabolic dysfunction may be the first indication of a degenerative cortical process in clinically diagnosed Alzheimer's disease, while cortical atrophy may become evident on CT and MR only late in the course of the disease. The typical pattern of glucose metabolism in early stages of Alzheimer's disease, however, is not yet understood clearly.

In this issue, Dr. Fukuyama and coworkers (*7*) added a new dimension to the understanding of energy metabolism in Alzheimer's disease. There was a general reduction in metabolic rates of glucose and oxygen in the temporoparietal and frontal regions. In Alzheimer's disease subjects, it has been previously reported that there is global and regional reduction of $CMRO_2$. Interestingly, Fukuyama et al. observed an abnormally high metabolic ratio ($CMRO_2$/CMRglu) in parietotemporal regions only, which suggests a metabolic shift from glycolytic to oxidative metabolism. They speculate that this change in metabolism is due to synaptic dysfunction as a result of impairment of glucose metabolism. This speculation links a decrease in glucose metabolism to acetylcholine depletion in Alzheimer's disease brains. The neurochemical evidence indicates that Alzheimer's disease can also be characterized as a primary degenerative condition of cholinergic terminals in the hippocampus and cortex. The neurotransmitter acetylcholine is very important in memory and learning. Since the hippocampus has a high concentration of cholinergic neurons, FDG-PET studies should also evaluate energy metabolism of the hippocampus, especially in early and probable Alzheimer's disease subjects.

These studies maintain one direction for PET research: emphasis on PET scanning methodology. To fully develop PET's scientific and clinical potential, however, PET scanning must reach out to methods and expertise beyond the scanning process to anatomical localization, behavioral tasks and the basic neurosciences. All three studies depend on manual or semiautomated methods to select regions of interest rather than use of either stereotactic localization or the superior method of MRI anatomic registration. None of these three studies use behavioral tasks to activate striatal motor centers or medial temporal memory areas. Lastly, these clinicians are tentative in focusing on the target regions suggested by the latest neuroscientific developments.

Dr. Vingerhoets et al. conclude that dopaminergic function in the whole striatum should be assessed concurrently because it gives slightly more reproducible data than the caudate or putamen separately, a viewpoint which substitutes reliability for validity. Dopaminergic function in striatal areas linked to the motor cortex or limbic system might have very different implications for Parkinson's disease.

Dr. Fukuyama et al. focus on the parietal cortex, which is identified as an area affected late in the course of Alzheimer's disease rather than the medial temporal region and hippocampus where neurofibullary tangles have been found to appear early. For example, in a postmortem study, Price et al. (*8*) observed that tangles "appear to expand progressively from the relatively restricted 'limbic' structures . . . to more widespread parts of the neocortex in severe dementia." Hof et al. (*8*) found "tangle formation restricted to selected areas of the temporal lobe" in an 82-yr-old woman who had mild signs of memory dysfunction in the months before death.

Behavioral technology combined with ongoing endeavors to achieve higher resolution with finer anatomical and functional localization are needed to fully exploit the bright neuroscientific future of PET.

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ERRATUM

Due to a production error, Figure 1 in the article "Comparison of Anatomically-Defined Versus Physiologically-Based Regional Localization Effects on PET-FDG Quantitation" by Resnick et al. (*J Nucl Med* 1993;34:2201–2207) was printed incorrectly. The corrected figure and legend is shown below.

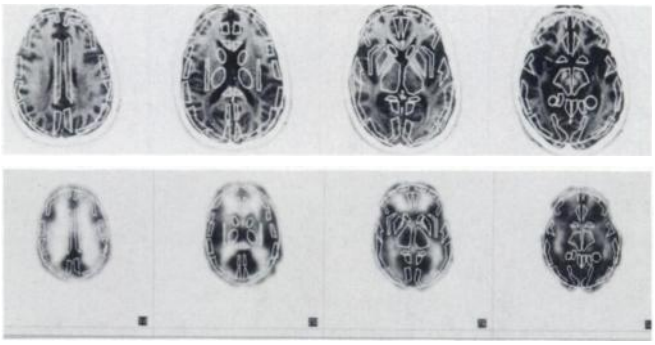

FIGURE 1. Adjusted template regions overlaid upon MRI (top) and corresponding PET (bottom) slices.