INVITED COMMENTARY

# Importance of Partial-Volume Correction in Brain PET Studies

Several neuroimaging studies have attempted to verify the neurophysiologic correlates of age-related changes in the brain. In the early 1980s, using the $^{133}$Xe inhalation method, researchers investigated cerebral blood flow (CBF) and reported significant reductions with age. Since these pioneering studies, which suffered from poor spatial resolution and other limitations, the advent of PET has provided neuroscientists with more sophisticated tools for the quantitative measurements of brain physiology. Conflicting results have been reached on the aging effect. The analysis of several parameters of cerebral function (including CBF, oxygen consumption, and cerebral blood volume) showed, on the whole, a linear decline with age. However, there was variability among these results, with age influencing some functional values more than others. On the other hand, some groups reported stability of brain physiologic parameters during healthy aging. For example, FDG PET studies in a particularly healthy group of elderly subjects showed no decline of glucose consumption with age (*1*,*2*). These inconsistencies were explained on the basis of different scanner resolutions or the method used to sample regions of interest (ROIs), as well as the control of behavioral and environmental variables.

In reviewing the literature, one has the impression of something lacking that could have affected the results. In the 1990s, investigators began to acknowledge the possible relationship among anatomic–structural changes related to aging and brain functional measurements; indeed, this was the case. Cerebral volume loss resulting from healthy aging processes can cause underestimation of PET physiologic measurements, despite great improvement in scanner resolution (*3*–*5*). Thus, the failure to account for the effect of partial-volume averaging of brains with expanded sulci has contributed to the confounding results in functional imaging studies of aging. Healthy aging of the brain can be characterized by FDG PET metabolic evaluation. Indeed, when brain atrophy and brain volume are considered, metabolic values no longer decline with age. This aspect has been further supported by PET metabolic studies of patients with Alzheimer's disease, in which the opposite has been clearly demonstrated: regional deficits in energy metabolism are not fully accounted by regional cerebral atrophy (*6*).

It is noteworthy that these original contributions continue to come from the same group. In this issue of *The Journal of Nuclear Medicine*, Meltzer et al., with a careful evaluation of MRI volume changes with respect to PET functional data, report no CBF decline with age in healthy individuals (*7*). Indeed, their work should serve as a guideline to the nuclear medicine field. They suggest the correction for the dilutional effect of age-related cerebral atrophy as mandatory in PET brain evaluations. They also suggest that other factors might influence the evaluation of resting cortical perfusion in aging. Among these, the cognitive level and the presence of cerebrovascular risks factors, which have been shown to be unaltered only in very-healthy elderly individuals, might indeed affect age-related brain functional decrease. As a consequence, these variables should be carefully considered in the research evaluation of elderly subjects.

The only true decline in regional CBF found by Meltzer et al. (*7*) after partial-volume correction was in the orbito-frontal cortex. This is consistent with other neuroimaging studies of aging (*8*,*9*). As suggested, these findings might reflect true functional changes with age in the prefrontal brain region, which could also explain the consistent changes in executive processes or mood in elderly persons.

Through other neuroimaging techniques, researchers are now ready to explore the biologic correlates of healthy aging and related changes in behavior. PET or functional MRI under specific cognitive activation can assess synaptic plasticity, which is clinically apparent as cognitive reserve capacity. In Alzheimer's disease, this is reduced when age-matched healthy individuals are compared and may be influenced by drugs that give support to neurochemical systems (*10*). It has also been recently suggested that regional cerebral glucose metabolism during audiovisual stimulation might be a more sensitive index of the functional–metabolic failure of neuronal systems than metabolism at rest (*11*). PET and radiolabeled tracers for receptor occupancy or enzymatic activities represent a unique tool for measurements of specific neurotransmission systems. With these methods, a decline of brain dopamine activity with age is well documented (*12*,*13*); more recently, a parallel loss of presynaptic and postsynaptic dopamine markers has also been shown (*14*). In healthy aging, the functional significance of dopaminergic changes has been related to indices of motor and cognitive function in specific neuropsychologic tasks that involve frontal lobe functions (*15*). This

Received Dec. 30, 1999; revision accepted Feb. 1, 2000.

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suggests that interventions may exist to enhance dopamine activity, which, in turn, may improve performance and quality of life for elderly individuals. Recently, a consistent decrease with age in 5HT2A receptors binding (with a 20% decline per decade starting at 30 y) has also been shown (*16*). Meltzer et al. (*17*), using $^{18}$F-altanserin, demonstrated a reduced binding to serotonin type 2 receptors, which persisted after partial-volume correction. These important discoveries on changes of neurotransmission systems create a new perspective in research related to therapeutic intervention for the aged brain.

In conclusion, functional brain imaging currently enables the localization and characterization of neural activity and biochemical events in the living human brain. In particular, the high sensitivity and selectivity of PET make it possible to probe neurochemical processes at the molecular level. The implications of these possibilities for the assessment of the effectiveness of therapeutic interventions in the field of normal and pathologic aging are only now starting to become clear. Meltzer et al. (*7*) suggest that future studies on the relationship among age, cerebrovascular risk factors, cognition, and mood changes, using PET methods, should always take into account the influence of the partial-volume effect on functional measurements.

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