SPECT Brain Imaging:  
The Role of Challenge Studies in Understanding Brain Function

Michael D. Devous, Sr., Ph.D.

Nuclear Medicine Center, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Most SPECT brain imaging studies reflect data obtained in the “resting” state. However, SPECT measurements of the brain’s response to challenge tests offer great promise in elucidating the extent and nature of disease, predicting outcome, or monitoring therapeutic response. Three types of challenges are used: cognitive, motoric and pharmacologic. Pharmacologic challenges offer the most promising avenue for understanding brain function through SPECT because they can be focused at very specific CNS functions. For example, acetazolamide, a potent cerebral vasodilator, can be used to determine vasodilatory reserve. Highly specific agonists and antagonists can be used to examine the responsiveness of particular receptor systems in humans. Cognitive challenges have been used to study frontal lobe function in schizophrenia and language function in normal and aphasic subjects. Motoric challenges have only been of limited value.

The most well-developed SPECT “challenge test” is the measurement of cerebrovascular reserve. It involves measuring regional cerebral blood flow (rCBF) before and after vasodilation with CO₂ or acetazolamide (Diamox). Normal vascular beds increase rCBF by 30–50%. Diseased or at-risk areas show little or no response. Reserve measurements are used to assess the need for acute interventions following stroke or transient ischemic attack, to assess risk status for secondary stroke, or to determine prognosis for postoperative outcome in AVM patients. Reserve measurements can also be used to determine whether resting rCBF alterations are of neuronal or vascular origin (e.g., to distinguish Alzheimer’s disease from vascular dementia).

Challenge studies, which require comparison of rCBF before and after the challenge, often use ¹³³Xe SPECT because ¹³³Xe rapidly clears from the body allowing rapid sequential imaging. “Static” rCBF tracers (e.g., ⁹⁹mTc HM-PAO or ¹²³I IMP) have prolonged brain retention times, requiring resting and challenge images to be obtained on occasions separated by 24–48 hours. Dual-isotope imaging, a recently developed technique of great use in SPECT challenge studies, permits simultaneous imaging of ⁹⁹mTc and ¹²³I labeled brain tracers administered to a single subject. We have reported the effectiveness of this technique in monitoring vasodilatory reserve, and dual-isotope studies are now being used for single-session cognitive or pharmaceutical challenge tests.

Challenge tests may be particularly useful in psychiatric disorders such as depression and schizophrenia. Typically, rCBF alterations in these disorders involve neuronal networks, which can now be identified by new three-dimensional image analysis techniques. Also, psychiatric patients characteristically have significant heterogeneity in their response to pharmacologic interventions. The diversity of responses has encouraged the use of neuroreceptor-specific agonists and antagonists in non-imaging challenge paradigms to enhance subcategorization of patients, to predict therapeutic response, and to identify state or trait markers which might be used in the prognostication of relapse. SPECT challenge studies should be similarly revealing. Already, Wolkin et al. have used PET to study the response to amphetamine in schizophrenic subjects. We have studied the relationship between SPECT measurements of rCBF and amphetamine-induced euphoria in normal controls and patients with depression.

Challenge studies should provide significant diagnostic and prognostic advantages and should enhance our basic knowledge of brain function. Nuclear medicine is poised to take advantage of the power and sophistication of such studies for three reasons: 1) improvements in tomographs (e.g., high resolution, dual-isotope imaging, and dynamic ¹³³Xe SPECT); 2) advances in rCBF and receptor ligands; and 3) evolving image analysis procedures. The future of SPECT challenge studies is bright.