Over the past 60 years, Mishkin has discovered some of the most important principles of brain organization, many of which are now considered much like established facts in the field of neuroscience. In the 1950s, for instance, while a student working with Karl Pribram, Mishkin identified the visual functions of the inferior temporal cortex through the study of lesions in the brains of monkeys. He established that this part of the brain is crucial for learning and retention of visual information. In the 1960s, Mishkin and Eichii Iwai showed that the posterior and anterior portions of the anterior temporal cortex were responsible for different types of visual functions, with the posterior handling perceptual aspects and the anterior playing a more important role in mnemonic aspects, such as recognizing a recently seen object. And in the 1980s, Mishkin and Leslie Ungerleider proposed that there were two visual systems within the primate brain—a ventral stream concerned with pattern vision ("what") and a dorsal stream concerned with spatial vision ("where"). This theory now provides the foundation for nearly all work on cortical visual processing.

In another important line of research, Mishkin has investigated the distinction between "cognitive" and "noncognitive" memories, both of which exist in animals and humans. Cognitive memories are those based on the integrity of the limbic system and are typically the ones associated with amnesia, such as being unable to recall an event or fact. Noncognitive memories are usually motor skills or habits, such as the ability to play a tune on the piano. By the mid-1980s, Mishkin and colleagues made the major discovery that the noncognitive habit system depends on the integrity of the basal ganglia. And as Acting Chief of the Laboratory of Neuropsychology at the National Institute of Mental Health, Mishkin continues to make major contributions to our understanding of amnesia, memories, and the brain.