Progress in elucidating the neural circuitry of the medial temporal lobe memory system, which includes the hippocampal formation (hippocampus plus entorhinal cortex), perirhinal and parahippocampal cortices, provides a dramatic example of how modern neuroanatomical investigations have contributed to an understanding of the function of the primate brain. It can now be confidently stated that all of the major inputs and outputs of the macaque monkey hippocampal formation, perirhinal cortex and parahippocampal cortex have been identified (Figure 1). Therefore, the sources of the “raw material” with which the hippocampal formation constructs episodic, declarative or relational memories (Eichenbaum and Cohen, 2001) are essentially known. It is also fair to say that there is far more detailed information on the neuroanatomical organization of the medial temporal lobe than on its physiology, particularly in the monkey. In fact, the details of the types and trajectories of information that traverse the pathways of the hippocampal formation and related structures provides functional predictions that have not yet been critically evaluated using electrophysiological or functional imaging techniques. Where neuroanatomical data has come into closest correspondence with functional data is in the design and interpretation of lesion studies that have sought to define the particular function of various components of the medial temporal lobe memory system. In the following paragraphs we will first describe the important role that neuroanatomical studies played in elucidating the structures important for memory in the medial temporal lobe. We will then comment on future directions of the role of neuroanatomy in this field.

An early and seminal finding in this field by Mishkin (1978) showed that bilateral lesions that included both the hippocampus and the amygdala in monkeys produced a profound memory impairment. This lesion was designed to resemble the presumed damage sustained by the profoundly amnesic patient H.M. (Scoville and Milner, 1957). Mishkin’s interpretation of this finding was that combined damage to both the hippocampus and the amygdala was essential to produce the severe H.M.-like memory impairment. In this same study, Mishkin also showed that damage to either the amygdala or hippocampus alone did not result in significant memory impairment. The implicit interpretation of this finding was that the amygdala and hippocampus could compensate for each other’s loss if only one structure was damaged. Given the strikingly different structural organization of these adjacent areas, this explanation was not entirely convincing. The clear and dramatic effect of the large medial temporal lobe lesion on memory, however, made this interpretation seem compelling at the time.

Studies by Zola-Morgan, Squire and colleagues in the 1980’s confirmed that large medial temporal lobe lesions that included both the hippocampus and the amygdala produced profound memory deficits (Zola-Morgan and Squire, 1985). However, further studies were undertaken to test the hypothesis that combined damage to the hippocampus and amygdala was required to produce a profound memory deficit. These studies revealed that while damage to the hippocampus produced a clear (though only moderately severe) memory deficit, the addition of a circumscribed amygdala lesion to the hippocampal lesion did not exacerbate the memory deficit resulting from hippocampal lesions alone (Zola-Morgan et al., 1989b). While these findings suggested that the hippocampus contributed importantly to memory, they also raised the possibility that damage to regions adjacent to the amygdala (but not the amygdala itself) were contributing to the deficit observed following the large medial temporal lobe lesions. But what were the regions of interest?

Key anatomical observations helped resolve this issue. Retrograde tracer studies by Insausti et al., (1987) examining the cortical afferents of the monkey entorhinal cortex, the major source of cortical input to the hippocampus, showed that this region receives nearly two-thirds of its cortical inputs from the adjacent perirhinal and parahippocampal cortices (PRPH cortices). These findings raised the possibility that the severe memory impairment seen after large medial temporal lobe lesions was due mainly to damage to the PRPH. Since these cortical areas were only partially damaged by lesions of the amygdala or hippocampus alone, perhaps it was only with concurrent damage to both structures that enough of the PRPH was damaged and severe memory impairment resulted.
To test this hypothesis directly, Zola-Morgan et al. (1989a) and Suzuki et al. (1993) examined the effects of bilateral lesions limited to the perirhinal and parahippocampal cortices (PRPH lesion) that spared the adjacent amygdala, hippocampus and entorhinal cortex. These experiments showed that the selective PRPH lesions produced a multimodal deficit that was similar in severity to the deficit observed following large medial temporal lobe lesions (Mishkin, 1978; Zola-Morgan and Squire, 1985). These findings together with other findings suggested that the PRPH cortices together with the hippocampal formation are the key structures mediating normal declarative/relational memory.

Thus, the anatomical studies focused on the entorhinal cortex provided key insight that helped resolve the controversies from the lesion findings. Anatomical studies focused on the perirhinal and parahippocampal cortices provided additional insight into precisely how these areas may be contributing to memory. Anterograde (Lavenex et al., 2002) and retrograde (Suzuki and Amaral, 1994) studies showed that the perirhinal and parahippocampal cortices form the major cortical gateways for sensory and multi-modal information both into and out of the rest of the hippocampal formation. The perirhinal cortex has its most prominent interconnections with the adjacent visual area TE, part of the ventral visual pathway, or “what” pathway. This observation suggested that the perirhinal cortex may be particularly involved in object memory, a prediction that is consistent with findings from lesion studies in monkeys (Gaffan, 1995; Buffalo et al., 1999). Other connections include somatosensory areas of the insula, orbitofrontal cortex, anterior cingulate cortex and parahippocampal cortex. These projections, taken together, suggest that the perirhinal cortex is a multimodal memory area involved in processing many different forms of memory.

The parahippocampal cortex, in contrast, receives its strongest inputs from cortical areas associated with the dorsal visual processing stream, or “where” pathway. These areas include the retrosplenial cortex, the dorsal bank of the superior temporal sulcus, posterior parietal cortex and the dorsolateral prefrontal cortex. These anatomical findings suggest that the parahippocampal cortex may be particularly involved in spatial memory. Consistent with this prediction, a growing number of functional imaging studies report clear hippocampal and parahippocampal activation during tasks of spatial and route memory (Aguirre et al., 1996; Shelton and Gabrieli, 2002).
FUTURE DIRECTIONS

The studies described above show how basic neuroanatomical data combined with lesion studies have helped to define the structures of the medial temporal lobe critical for memory. The next level of analysis is to understand how particular neural circuits within the medial temporal lobe mechanismically support memory. An even more refined level of neuroanatomical analysis will be needed to address this question. For example, information about the intrinsic connections of the individual medial temporal lobe areas will provide insight into how these areas communicate with each other. Immunohistochemical information is already providing information on the distributions of various neurochemical markers including proteins associated with inhibitory neurotransmission throughout the medial temporal lobe (Suzuki and Porteros, 2002). Combining immunohistochemical staining, tract-tracing and electron-microscopic studies will allow us to define the intrinsic and extrinsic projection of immunohistochemically defined subpopulations of neurons. Only by understanding both the excitatory and inhibitory circuits of the medial temporal lobe will we ultimately understand how neurons in these areas mediate memory.

In conclusion, neuroanatomical information has played a central role in our understanding of the organization of the medial temporal lobe memory system. The neuroanatomical studies described above have led the way in defining brain regions involved in memory and have challenged electrophysiological and functional imaging approaches to attach functional significance to the myriad pathways that have been described. We are now entering an extraordinarily exciting epoch when functional analyses are starting to clarify the significance of some of the defined neuroanatomical pathways of the medial temporal lobe and will ultimately challenge us to delve even deeper into the neuroanatomical organization of this region.