# 24

# The Perirhinal, Entorhinal, and Parahippocampal Cortices and Hippocampus: An Overview of Functional Anatomy and Protocol for Their Segmentation in MR Images

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## Abbreviations

| | |
|---|---|
| A | Anterior |
| Ab | Angular bundle (PHg white matter) |
| aCf | Anterior calcarine fissure |
| AD | Alzheimer's disease |
| al | Alveus |
| Am | Amygdala |
| bG | Band of Giacomini |
| cf. | Crus of the fornix |
| Cs | Collateral sulcus |
| di | Hippocampal digitations |
| ERc | Entorhinal cortex |
| Fg | Fusiform gyrus |
| fi | Fimbria |
| gA | Gyrus ambiens |
| gS | Gyrus of Schwalbe |
| HB | Hippocampal body |
| Hf | Hippocampal fissure |
| HH | Hippocampal head |
| Hs | Hippocampal sulcus |
| HT | Hippocampal tail |
| I | Inferior |
| ILg | Intralimbic gyrus |
| Is | Isthmus |
| ITg | Inferotemporal gyrus |
| L | Laterial |
| Lg | Lingual gyrus |
| li-gm | Limen insulae gray matter |
| li-wm | Limen insulae white matter |
| M | Medial |
| Mb | Mammillary body |
| MTL | Medial temporal lobe |
| OTs | Occipitotemporal sulcus |
| P | Posterior |
| PHc | Parahippocampal cortex |
| PHg | Parahippocampal gyrus |
| PRc | Perirhinal cortex |
| Pu | Pulvinar |
| qgc | Quadrigeminal cistern |
| Rs | Rhinal sulcus |
| S | Superior |
| SAs | Semiannular sulcus |

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| | |
|---|---|
| SLg | Semilunar gyrus |
| Sp | Splenium |
| su | Subiculum |
| TLV | Temporal horn of lateral ventricle |
| TP | Temporal pole |
| TR | Transentorhinal cortex |
| U | Uncus |
| Ug | Uncinate gyrus |
| un | Uncal notch |

## 24.1 Introduction

Medial temporal lobe (MTL)) damage severely disrupts our ability to form new memories (Scoville and Milner 1957). Indeed, memory dysfunction is the hallmark of Alzheimer's disease (AD; e.g., Salmon 2011), a progressive neurodegenerative disorder which begins in and most prominently affects the MTL region (Braak and Braak 1991). Accordingly, the classical model of memory claims that the MTL functions as a single system subserving memory formation and not other kinds of cognitive processes (Squire and Zola-Morgan 1988; Squire and Zola 1998; Squire and Wixted 2011).

Converging evidence from animal and human cognitive neuroscience research suggests a more differentiated picture, one of functional diversity in the MTL subregions (e.g., Lee et al. 2005; Davachi 2006). Thus, in addition to supporting the formation of memories, each MTL subregion may also perform other specific functions. A first section briefly describes the putative specialized functional roles of the MTL subregions, namely, the perirhinal cortex (PRc; Broadmann areas [BA] 35/36), the entorhinal cortex (ERc; BA 28/34), the posteriorly situated parahippocampal cortex (PHc; BA 36; also known as posterior parahippocampal cortex), and the hippocampus proper, highlighting recent findings from animal and human cognitive neuroscience research.

The functional neuroanatomy of the MTL, including but not limited to the domain of memory, has implications for the clinical interpretation of circumscribed MTL lesions as well as the interpretation of functional impairments in patients with neurodegenerative disorders, most notably AD. A second section, therefore, describes the neuropsychology of the early AD syndrome including amnestic mild cognitive impairment (aMCI; Winblad et al. 2004).

The prerequisite for advancements in this important area of research is the valid and reliable identification of these regions on structural brain imaging scans. Indeed, many of the controversies in current human neuropsychological research may stem from inadequate control of lesion extent and location, as noted by Squire and Wixted: "The importance of thorough neuroanatomical measurement in neuropsychological studies of memory cannot be overstated. Many current disagreements about the facts and ideas emerging from neuropsychological research on human memory can be traced to concerns about the locus and extent of lesions. […] There is no substitute for thorough, quantitative descriptions of damage based on magnetic resonance imaging, as well as (where possible) detailed neurohistological description of the postmortem brain" (Squire and Wixted 2011, p. 268). The identification of MTL subregions is challenging because of the uncertainty or obscurity of anatomical landmarks, a difficulty compounded by the fact that some MTL gyri and sulci are interindividually highly variable. A third section, therefore, describes the gross anatomy of the MTL and, building upon previous seminal work of especially Insausti and colleagues (Insausti et al. 1998), presents a method for delineating the PRc, ERc, PHc, and the hippocampus proper on structural MR images (see also Watson et al. 1992; Insausti et al. 1998; Pruessner et al. 2000; Van Hoesen et al. 2000; Vogt et al. 2006; Malykhin et al. 2007; Taylor and Probst 2008; Van Hoesen 1995).

## 24.2 Functional Neuroanatomy of the MTL

The MTL has been irrevocably linked with the formation of long-term memory traces since Scoville and Milner's (Scoville and Milner 1957) description of the patient H.M., who became severely amnesic following an experimental

bilateral MTL resection to treat his intractable epilepsy. H.M.'s surgical lesion included the intraventricular portions of the bilateral hippocampi (see Fig. 24.7), the amygdalae, and the medial temporal poles and extended laterally to the ERc, with relative sparing of the PRc and PHc (Corkin et al. 1997). Following the procedure, H.M. suffered from a persistent and profound anterograde amnesia, that is, an inability to remember events occurring after the operation, and a temporally graded retrograde amnesia, that is, difficulty remembering events that occurred within the 11 years preceding the MTL resection. He also suffered from partial anosmia, a lack of initiative and emotional bluntness (Corkin 1984). Strikingly, H.M.'s intellectual functions were relatively preserved, as were other forms of memory such as perceptual and motor skill learning, priming, habit formation, working memory, and memories for facts, events, and verbal semantic memories remote from his surgery (Corkin 1984). These functions enabled him to perform normally in many tasks including his avid crossword puzzle hobby (Skotko et al. 2008).

Cases such as H.M. were remarkable on many fronts. Most importantly, they demonstrated that memory indeed had a circumscribed anatomic basis in the MTL (*cf.* Lashley 1929).[1] It became clear that the type of memory typically affected in the MTL amnesia syndrome was the acquisition of declarative memories, that is, explicit memories of events from an individual's autobiography (episodic memory) and for facts and world knowledge (semantic memory), all of which are available to conscious awareness. The case of H.M. also sparked intensive work on rodents and nonhuman primates. The strategy used in this research was to ablate cytoarchitectonically distinct regions of the MTL and measure ensuing memory performance, research which critically relied on the delayed (non) matching-to-sample recognition memory paradigm.[2] This work led to the development of an animal model of amnesia where bilateral lesions of the hippocampus, parahippocampal gyrus, and amygdala were associated with severe recognition memory impairments with otherwise apparently preserved cognitive functions (Mahut et al. 1982; Mishkin 1978). More specific ablation studies refined these early results by demonstrating that lesions restricted to the hippocampus (Mahut et al. 1982; Zola-Morgan et al. 1989a; but see also Murray and Mishkin 1998) or to the parahippocampal gyrus (Zola-Morgan et al. 1989c; Meunier et al. 1993), but not amygdala (Zola-Morgan et al. 1989b) or mammillary bodies (Aggleton and Mishkin 1985), were sufficient to produce a severe recognition memory disorder. Moreover, the effects of lesions to different subregions appeared to be additive, and the most severe recognition memory impairment was measured following PRc lesions (Meunier et al. 1993; Zola-Morgan et al. 1989b). Drawing on these seminal experiments, Squire and colleagues developed the classical, single-process model of human memory functioning, which posited that the MTL subregions represent a single memory system in which each area is critical for forming declarative memories but do not participate in other cognitive functions (Zola-Morgan et al. 1986; Squire and Zola-Morgan 1988; Squire and Zola 1998; Squire and Wixted 2011). This classical, single-process model of MTL function has remained highly influential.

The field of MTL research has since burgeoned and now uses multimodal imaging methods with increasingly more detailed cognitive paradigms to study multidimensional aspects of MTL functioning. This work has led many authors to reconceptualize the MTL as a group of functionally specialized subregions (Mishkin et al. 1997; Aggleton and Brown 1999; Lavenex and Amaral

[1] Later research demonstrated that profound memory impairments were also associated with damage to diencephalic regions such as mammillary bodies or mediodorsal nucleus of the thalamus (Squire and Zola-Morgan 1988; Victor et al. 1989), although the nature of the memory impairment differed from amnesia following MTL damage.

[2] In these experiments, an animal is presented with a sample stimulus during a learning phase. After a delay, the sample stimulus is presented again together with a novel stimulus. Intact recognition memory is demonstrated by the animal displacing either the sample object (delayed matching to sample) or the novel object (delayed nonmatching to sample).

2000; Davachi 2006; Henke 2010; Montaldi and Mayes 2010; Ranganath 2010), with different models emphasizing different aspects of functional specialization. For example, the two-process model argues for specialized memory functions within the MTL, with the PRc supporting context-free item familiarity (i.e., a feeling of knowing that an item was previously encountered) and the hippocampus and PHc explicit, context-rich item recollection (Aggleton and Brown 1999, 2006; Brown and Aggleton 2001; Yonelinas 2002; Montaldi and Mayes 2010). Other authors highlight functional-neuroanatomical relationships specific to object and spatial information processing (e.g., Davachi 2006; Lee et al. 2008) or item and relational information processing (e.g., Eichenbaum et al. 1999; Davachi and Wagner 2002; Davachi 2006; Henke 2010). Common to these models is the idea that while the entire network of highly interconnected subregions is typically engaged during declarative memory formation, each subregion may be specialized for processing a unique aspect of the event or concept (for reviews, see, e.g., Aggleton and Brown 1999, 2006; Eichenbaum et al. 1999, 2007; Squire et al. 2004; Moscovitch et al. 2005; Henson 2005; Davachi 2006; Henke 2010; Montaldi and Mayes 2010, 2011; Kravitz et al. 2011).

Many researchers of MTL function rely on an anatomically driven connectivity approach based on nonhuman primate data (Mishkin et al. 1983; Lavenex and Amaral 2000) to generate novel hypotheses of human MTL function. Nonhuman primate MTL connectivity demonstrates that each subregion receives information from different sensory and polymodal cortices and integrates the information it receives in intrinsic associational connections and in a hierarchical system from the PRc and PHc to the ERc and from the ERc to the hippocampus (Mishkin et al. 1983, 1997; Lavenex and Amaral 2000). The first basic premise of this account is that each MTL subregion is specialized to process the information it receives and integrates in intrinsic associational connections (Lavenex and Amaral 2000; Lavenex et al. 2004). The second basic premise is that each processing level – from PRc/PHc to ERc and from ERc to the hippocampus – is characterized by an increasing amount of convergence of information and a higher level of associativity of the coded representation (a "hierarchy of associativity"; Lavenex and Amaral 2000). Further, we outline the functional neuroanatomy of the PRc, PHc, ERc, and hippocampus based on this approach.

The *perirhinal cortex* receives prominent afferents from the ventral visual object-processing stream (the "what" stream) and less dense inputs from other unimodal and polymodal sensory systems, the orbitofrontal, insula, and cingulate cortex (Suzuki and Amaral 1994a). Tracing studies have also demonstrated a rich network of intrinsic associational connections within the PRc, which presumably bind this multimodal information together (Lavenex et al. 2004). In line with this connectivity pattern, numerous animal lesions studies have demonstrated that the PRc plays an essential role in visual object recognition memory (Meunier et al. 1993; Zola-Morgan et al. 1989c) and multimodal object memory (e.g., by forming flavor-visual and tactile-visual associations; see Murray and Richmond 2001; Murray et al. 1998 for overviews). Bussey, Saksida, Murray, and colleagues suggested that the PRc represents the apex of the ventral occipital-temporal visual processing pathway, which computes increasingly more complex combinations of visual features from posterior to anterior sites. Thus, the PRc may be engaged during demanding visual perceptual task, e.g., discriminating between objects who share many features with one another (Bussey and Saksida 2002; Bussey et al. 2005).

Research on human PRc functioning has been hampered by the paucity of naturally occurring lesions restricted to this region, although PRc damage does occur in the context of more widespread lesions. Moreover, fMRI studies are confronted with signal dropout around the PRc due to nearby air-tissue interfaces which induce susceptibility artifacts in gradient-echo sequences (Cusack et al. 2005; Schmidt et al. 2005; Bellgowan et al. 2006; Schwarzbauer et al. 2010). Nonetheless, converging evidence from human functional imaging and patient studies broadly support the nonhuman primate findings described above. In fMRI studies, PRc activity in

healthy controls has been associated with memorizing individual items (Davachi and Wagner 2002), changes in object identity (Pihlajamäki et al. 2004; Köhler et al. 2005; O'Neil et al. 2009), fine-grained analyses of visual objects (Tyler et al. 2004), the recognition of ambiguous visual objects (Moss et al. 2005), demanding visual discrimination tasks (Barense et al. 2005), and the integration of object features from different sensory modalities (Taylor et al. 2006). In the same vein, patients with brain damage in the parahippocampal gyrus including the PRc were impaired in discriminating highly similar, complex visual stimuli (Barense et al. 2007, 2010; Moss et al. 2005) and integrating crossmodal object features (Taylor et al. 2009, 2011a), even in the absence of memory demands. Finally, difficulties in visual object recognition memory were observed in patients with aMCI (Barbeau et al. 2004), commonly considered a possible AD prodrome with putative PRc pathology (Braak and Braak 1991).

The nature of information integrated in the PRc – multimodal and potentially non-sensory motivational features (Liu et al. 2000) associated with individual objects – has led some authors to suggest that the PRc codes for semantic object memories, that is, our knowledge about individual objects (Murray and Richmond 2001). For example, despite H.M.'s profound amnesia, he was able to acquire fragments of conceptual information, a feat attributed to his relatively intact PRc (*cf.* Corkin et al. 1997). When presented with the names of people who became famous after his MTL resection, H.M. was able to correctly distinguish these names from unfamiliar foil names, showing only a mild impairment relative to control participants (O'Kane et al. 2004). In an influential study, Vargha-Khadem et al. (1997) studied four patients with selective hippocampal damage acquired at an early age, who were nonetheless able to acquire normal levels of language comprehension and perform relatively well in school, that is, acquire semantic-like knowledge. Thus, although these individuals were significantly impaired at encoding the events in their lives, they were able to acquire world knowledge (semantic memories), an ability attributed to the intact parahippocampal gyrus (Mishkin et al. 1997; Vargha-Khadem et al. 1997).

MRI studies in humans provide additional support for the role of the PRc in processing the meaning of individual objects: fMRI studies showed that PRc activity was related to the meaning of object stimuli (Moss et al. 2005; Taylor et al. 2006; see also Wang et al. 2010), while voxel-based correlation studies (Hirni et al. 2011; Taylor et al. 2011b) and a cortical thickness study (Kivisaari et al. 2012) demonstrated significant relationships between gray matter integrity in the MTL, including the PRc and performance on semantic object tasks. Semantic object processing in the PRc may also manifest itself as the feeling of familiarity about having previously encountered an object in the absence of recall about specific contextual details (two-process models; see Eichenbaum et al. 2007; Montaldi and Mayes 2010 for reviews). Taken together, these findings suggest that the PRc integrates the visual and multimodal information it receives to support complex visual discriminations (Bussey et al. 2002, 2005) and to form visual and multimodal memories of meaningful objects, that is, semantic object memories.

The *parahippocampal cortex* lies posterior to the PRc and receives afferent projections primarily from the dorsal ("where") processing system in the posterior parietal cortex (Suzuki and Amaral 1994a). This "parieto-medial temporal pathway" has been implicated in visuospatial processing (Kravitz et al. 2011). It begins in the posterior inferior parietal lobule and sends direct connections to the PHc and hippocampus as well as indirect connections via the posterior cingulate and retrosplenial cortices to the PHc and same hippocampal fields. Thus, the PHc is attributed a central role in processing visuospatial and landmark information. Accordingly, in nonhuman primate studies, PHc damage has been linked with the impaired recognition of novel object locations and object-place associations (Alvarado and Bachevalier 2005a; Bachevalier and Nemanic 2008).

Findings from human functional imaging studies suggest that also the human PHc processes spatial and navigational information

(Köhler et al. 2002, 2005; Buffalo et al. 2006; Staresina et al. 2011). For example, Pihlajamäki et al. (Pihlajamäki et al. 2004) demonstrated heightened PHc (and posterior hippocampal) activation when participants processed novel spatial arrangements of familiar objects, in contrast with the processing of novel objects in the same spatial arrangement. Evidence for a role of the PHc in landmark processing in healthy participants was provided by Maguire et al. (1998), who found heightened PHc metabolism when participants navigated in virtual environments with salient objects and textures compared to when they navigated in empty environments. Similarly, Burgess and colleagues (Burgess et al. 2001) showed increased BOLD activation in the PHc when participants recalled landmarks from memory and in the absence of spatial scene information. Moreover, Epstein and Kanwisher (Epstein and Kanwisher 1998) observed that posterior parts of the bilateral parahippocampal gyri extending into the lingual gyri were preferentially activated when participants observed real or artificial visual scenes, with attenuated activity during the viewing of objects, faces, or scrambled scenes. These relationships prompted Kanwisher and colleagues to label an area in the posterior PHc displaying these characteristics as the parahippocampal place area (PPA; Epstein and Kanwisher 1998; Epstein et al. 1999; see also Grill-Spector and Malach 2004). These studies suggest that PHc processes both perceptual and mnemonic features of its preferred stimuli, that is, the spatial arrangement of objects or landmarks, which underpin our ability to navigate in the environment.

Other authors have suggested that the PHc processes not just spatial landmark or scenic stimuli and memories but more abstract information related to these stimuli (Diana et al. 2007). For example, BOLD activity in the PHc was stronger in response to strongly semantically related object-scene pairs (e.g., a driving wheel inside a car) compared to weakly semantically related object-scene pairs (e.g., a purse on a table; Bar et al. 2008). Bar and colleagues also found heightened PHc activity in response to objects which were strongly associated with a particular environment (e.g., a roulette wheel or beach chair as opposed to a cherry or basket), in the absence of an explicit spatial stimulus (Bar and Aminoff 2003). The sensitivity of the PHc to the meaningfulness of the visuospatial stimuli resembles the PRc's ability to code for the meaning of its preferred stimulus, that is, objects (see above).

Damage to the human PHc results in a pattern of deficits consistent with the functional imaging studies reported above, specifically in the syndrome of topographical disorientation. Two variants of topographical disorientation are recognized: landmark agnosia and anterograde topographic disorientation (Paterson and Zancwill 1945; Whiteley and Warrington 1978; De Renzi 1982; Barrash 1998). Damage to the posterior PHc is associated with landmark agnosia, in which patients are unable to recognize famous or familiar environmental stimuli such as buildings, statues, or scenes (Epstein et al. 1999; Takahashi et al. 2002). These agnostic impairments lead to difficulties navigating the environment despite normal topographical memory and spatial processing ability (Aguirre and D'Esposito 1999). Patients with anterograde topographic disorientation (also known as topographical amnesia; De Renzi et al. 1977) following unilateral or bilateral PHc lesions have difficulties forming representations of new environments, with otherwise intact visuospatial functioning (Barrash 1998; Barrash et al. 2000; Bohbot et al. 2000). These patients are, therefore, also unable to orient and navigate in new environments but may successfully navigate in premorbidly familiar environments. Thus, these findings further support the view that the PHc is primarily involved in the perceptual and mnemonic processing of scenes, that is, the visuospatial arrangement of landmarks, and potentially their meaning, functions which enable orientation and navigation in the world.

The PRc and PHc send afferents to the *entorhinal cortex*, which receives less dense inputs from the amygdala, olfactory structures (e.g., piriform cortex, olfactory bulb), insula and frontal cortex, basal forebrain, thalamus, basal ganglia, and brainstem (Insausti et al. 1987; Suzuki and Amaral 1994b; Canto et al. 2008). A striking feature of the PRc and PHc afferents in the rodent and nonhu-

man primate ERc is the topographical segregation of their terminations: the anterolateral aspects of the nonhuman primate ERc receive highly integrated visual information via the PRc (Suzuki and Amaral 1994a, 1994b), whereas the posteromedial aspects of the ERc receive information primarily from the parieto-medial temporal visuospatial pathway via the PHc (Suzuki and Amaral 1994a, 1994b; Canto et al. 2008; Kravitz et al. 2011). Notably, in rodents and nonhuman primates, the segregation of inputs is largely preserved in the intrinsic connectivity of the ERc (Dolorfo and Amaral 1998; Chrobak and Amaral 2007).

The afferent and intrinsic pattern of ERc connectivity suggests a relative segregation of object and spatial information processing in the anterolateral and posteromedial ERc, respectively. While largely unexplored in nonhuman and human primates, rodent research partly supports this functional-neuroanatomic division of labor. For example, cells in the rodent ERc receiving prominent visuospatial inputs show high spatial tuning, whereas cells in other ERc regions are only weakly modulated by spatial changes (Fyhn et al. 2004). Furthermore, lesions specifically in this spatially tuned area in the rodent ERc have been associated with spatial, navigational impairments (Steffenach et al. 2005). Perhaps most strikingly, a subgroup of cells in this region shows a high degree of spatial sensitivity when rats run freely in an open environment: these "grid cells" fire regularly as the rat traverses vertices of an imaginary grid of tessellated triangles mapped onto allocentric physical space (Hafting et al. 2005).[3] The dynamics of the population of grid cells may support "path integration," that is, the ability to determine one's current position relative to a starting point based on self-generated movement, as opposed to environmental cues (Witter and Moser 2006; Hasselmo and Brandon 2008). A potential segregation of ERc function has not yet been explicitly tested in primates (but see Suzuki et al. 1997).

A specific role of the anterolateral ERc in object processing, as implied by its prominent PRc inputs, has not been definitively established. However, the entire ERc has been strongly implicated in object recognition memory. Animal lesion studies show that object recognition impairments, albeit mild, can follow selective ERc lesions (Leonard et al. 1995; Meunier et al. 1993) and that concomittant lesions of the PRc and ERc exacerbate the object recognition impairments found with selective PRc lesions (Meunier et al. 1993). A functional imaging study with healthy human participants demonstrated greater ERc activation during rote learning of words compared to the relational processing of words, supporting the role of human ERc in processing of single items (Davachi and Wagner 2002). Given the resolution of common fMRI studies, and the additional effects of Gaussian smoothing enabling group analyses, future human studies addressing this question will require high-resolution fMRI (Carr et al. 2010) in conjunction with refined behavioral tasks.

The most striking impairment following damage to the entire human ERc is episodic memory dysfunction (Eustache et al. 2001; Di Paola et al. 2007; Coutureau and Di Scala 2009). These lesions typically extend beyond the ERc into the hippocampus, such that it is not known whether isolated ERc lesions are sufficient to impair episodic memory functioning. Rather than focusing on the types of information processed or integrated in the ERc, recent studies of episodic memory functioning and the ERc focus on the electrophysiological properties of its neurons, which provide key information about how episodic memories, are formed in downstream hippocampus. Specifically, in computational models, persistent firing upon depolarization and the oscillations of the dendritic membrane

[3]It is tempting to hypothesize similar grid cell properties for human ERc neurons. To our knowledge, a single human fMRI study has found evidence consistent with this hypothesis. Doeller and colleagues (Doeller et al. 2010) found that BOLD activity in the human ERc had a sixfold sinusoidal relationship with "running" direction in a circular-shaped virtual environment. This pattern of activation corresponds to the symmetry of grid cell firing in rodent ERc and putatively reflects whether the participants ran in alignment or misalignment with the grid axes. The ERc was activated as part of a larger network showing these properties, which included the posterior and medial parietal, lateral temporal, and medial prefrontal cortices (Doeller et al. 2010; see also Jacobs et al. 2010).

potential of some ERc neurons may give rise to cyclical and graded firing patterns which support information binding in downstream hippocampus (Hasselmo and Brandon 2008; Wallenstein et al. 1998; see also Fyhn et al. 2007; Lipton and Eichenbaum 2008). In summary, the ERc appears to be involved in both object and spatial processing, although evidence for the anatomical segregation of these processes within the human ERc remains elusive. More evidence from lesion studies exists to suggest that ERc, together with the hippocampus, is critical for the formation of episodic memories, that is, the binding together of contextual and associative information with an object or scene. The ERc's specialized role in episodic memory formation may be reflected not only in the information content delivered by its afferent connections but also by the electrophysiological properties of its neurons.

The perforant pathway connects the ERc with the *hippocampus proper*, with primary projections to the dentate gyrus and weaker projections to the CA1 and CA3 subfields and the subiculum (Witter 2007). Nonhuman primate studies demonstrate that the pathway between the ERc and dentate gyrus has two main components: one set of connections links anterolateral ERc (which receives its primary input from the visual object-processing system via the PRc) with the intermediate and posterior parts of the hippocampus and a second set links posteromedial ERc (the primary termination of PHc efferents coding spatial information) primarily with the posterior hippocampus (e.g., Witter and Amaral 1991; Witter 2007; see also Dolorfo and Amaral 1998). The most anterior parts of the hippocampus receive afferents from forebrain structures such as the amygdala and hypothalamus via the ERc and have been hypothesized potentially mediate endocrinological functions including stress-related physiological responses (Moser and Moser 1998).

Evidence of an anterior-posterior gradient of functional specialization implied by this connectivity pattern has indeed been demonstrated in several animal and human studies. Activation in the anterior extent of the hippocampal body has been demonstrated in response to judging object novelty (Pihlajamäki et al. 2004) and during a crossmodal object-processing task (e.g., Taylor et al. 2006). Similarly, lesions including the anterior hippocampi are associated with object-processing impairments (Barense et al. 2005; Acres et al. 2009; Taylor et al. 2009). Conversely, research on rats suggests relative specialization of the rodent homologue of posterior hippocampus to spatial processing. For example, the highly spatially tuned "place cells" (for reviews, see Eichenbaum et al. 1999; Burgess et al. 2002) are more prevalent in the rodent homologue of posterior compared to anterior primate hippocampus (Jung et al. 1994).[4] Correspondingly, lesions of the rodent homologue of the posterior hippocampus disrupt spatial learning (Colombo et al. 1998; for a review, see Moser and Moser 1998). Although subsequent research has failed to demonstrate place-like cells in the primate hippocampus, the posterior hippocampus nevertheless appears to contribute to spatial processing in primates (Alvarado and Bachevalier 2005b). For example, in human functional imaging studies, spatial tasks elicited activity in the posterior parts of the human hippocampus (e.g., Pihlajamäki et al. 2004), and a morphometric MR study demonstrated more voluminous posterior hippocampi in London taxi drivers with a highly developed spatial abilities (Maguire et al. 1998).

A higher-order anatomical characteristic of the hippocampus, beyond the hypothesized anterior-posterior gradient of functional specialization, is its location at the top of the MTL processing hierarchy (Lavenex and Amaral 2000). This position confers the ultimate integration ability on the hippocampus, functions presumably supported by intrinsic connectivity both longitudinally and mediolaterally (Witter 2007). Thus, the hippocampus has been suggested to bind multisensory object and spatial, contextual, and associational information together to repre-

[4]The original discovery of "place cells" demonstrated that these cells selectively fired according to the animal's location in the environment (O'Keefe and Dostrovsky 1971), while later studies showed that firing patterns were also modulated by other factors such as motivational factors and environmental cues (Lipton and Eichenbaum 2008; see Eichenbaum et al. 1999 for a review).

sent our semantic and episodic memories, also more generally known as "relational memories" (Henke et al. 1997; Eichenbaum et al. 1999; Burgess et al. 2002; Davachi and Wagner 2002; Davachi 2006). In its basic form, these memories bind both spatial and context information from the dorsal stream, transmitted via PHc-ERc connections (Kravitz et al. 2011), together with object information received via PRc-ERc connections (Suzuki and Amaral 1994a). Critically, the primate hippocampus additionally integrates higher-order, more abstract information related to objects and episodes together. For example, the nonhuman primate hippocampus was shown to be involved in a transverse patterning task which requires the formation of indirect associations between items (e.g., A is rewarded with B, B is rewarded with C, but A is not rewarded with C or B with A; Alvarado et al. 2002; Alvarado and Bachevalier 2005b). In human functional imaging studies, the hippocampus was activated during the formation of higher-order, semantic associations (Henke et al. 1997, 1999b; Davachi and Wagner 2002), upon presentation of novel spatial organization of objects or novel combination of familiar objects and familiar locations (i.e., Köhler et al. 2005) and object-space relationships (Hannula and Ranganath 2008). These findings are consistent with the clinical sequelae of isolated hippocampal lesions, that is, the classic amnesic syndrome. Such lesions may occur following carbon monoxide poisoning (Zola-Morgan et al. 1986; Vargha-Khadem et al. 1997; Henke et al. 1999a; Gadian et al. 2000), which causes cellular damage in the CA1 subfield of the hippocampus through hypoxic and histotoxic mechanisms (O'Donnell et al. 2000; Gale and Hopkins 2004). Patients with isolated hippocampal lesions display an anterograde amnesia for episodic memories with otherwise relatively normal cognitive functioning, similar to H.M. (see above; Vargha-Khadem et al. 1997; Zola-Morgan et al. 1986), although the magnitude of the impairment may be milder than that following more widespread MTL lesions (Zola-Morgan et al. 1986).

Recent models of hippocampal functioning emphasize its pattern separation and pattern completion abilities (Rolls 2007; Yassa and Stark 2011). Pattern separation is the appreciation of slight differences between sensory input and existing representations, a function which presumably enables the acquisition of distinct and complex representations corresponding to human episodic memories. The dentate gyrus and the CA3 of the hippocampus proper appear to be critically involved in rodent pattern separation (Leutgeb et al. 2007; Rolls 2007; see Yassa and Stark 2011 for a review), and this process is thought to be modulated by neurogenesis in the dentate gyrus (Deng et al. 2010). Tentative evidence for pattern separation functions in the human dentate gyrus and CA3 was provided by a high-resolution fMRI study by Bakker and colleagues (Bakker et al. 2008). These investigators presented participants with pictures of objects that were either novel, repeated, or slightly modified pictures of the repeated objects (lures). An area encompassing the DG and CA3 showed enhanced patterns of activity to novel and lure objects and weaker responses to object repetitions, suggesting that human DG and CA3 detect subtle differences between sensory input and existing representations. The process of pattern separation is hypothesized to be balanced by pattern completion, that is, the ability to recollect an existing representation on the basis of an incomplete set of cues (O'Reilly and McClelland 1994). This process is thought to be supported by ERc afferents bypassing the dentate gyrus, which may introduce the cue to CA3 to reactivate an existing representation, as well as auto-associative recurrent connectivity in CA3 (Leutgeb et al. 2007; Rolls 2007; Yassa and Stark 2011). The complementary processes of pattern separation and pattern completion may give rise to the capacity of human memory to treat highly similar episodes, such as events in the office on last Monday and Tuesday, as distinct from one another (pattern separation) while enabling the retrieval of a memory based on incomplete information, for example, remembering what took place on Monday based on knowing that a chocolate cake was available during the coffee break (pattern completion).

Taken together, animal and human studies demonstrate that the hippocampus, together with the ERc, binds information across spatial and temporal intervals, ultimately giving rise to complex, multicomponential semantic and episodic memories. These processes take place extremely rapidly and may even proceed in the absence of conscious awareness (Henke 2010). Pattern separation and completion processes in the hippocampus may represent fundamental processes supporting memory formation and retrieval, enabling the prerequisite disambiguation of phenomena and successful retrieval based on fragmentary cues, respectively.

## 24.3 Alzheimer's Disease and Other Dementias Associated with the MTL

AD is a debilitating neurodegenerative condition which globally affects 3.9% of the individuals over 60 years of age (Qiu et al. 2009). Since the risk of developing AD is strongly linked with increasing age, and given our increasing life expectancies, the prevalence of AD is expected to exponentially increase in the upcoming decades, tripling between 2010 and 2050 (Alzheimer's Association 2011). The clinical diagnosis of probable AD requires the presence of a memory impairment in addition to an impairment in one other domain of cognitive functioning (i.e., language, praxis, gnosis, and executive functions), which is severe enough to affect everyday functioning (American Psychiatric Association 1994). The definite diagnosis of AD is made upon autopsy, where it is characterized by two neuropathological hallmarks: the accumulation of amyloid β-peptide (Aβ) as plaques in the extracellular space in widespread regions of the brain and the formation of insoluble aggregates of hyperphosphorylated isoforms of microtubule-associated tau-proteins (Mattson 2004; Ewers et al. 2011). These abnormal isoforms of tau form neurofibrillary tangles in the nerve cells.

The distribution of neurofibrillary tangle deposition typically follows a sequential progression in the cerebral cortex (Braak and Braak 1991). Correspondingly, the stage of neurofibrillary pathology correlates with cognitive dysfunction, whereas the relationship between Aβ plaques and cognition is less clear (Ghoshal et al. 2002; Guillozet et al. 2003). Neurofibrillary tangles first affect the transentorhinal cortex (TR) of the PRc, from where they spread to the ERc and hippocampus proper and then to the neocortex (Braak and Braak 1985, 1991). Notable exceptions to this pattern exist, for example, a rare "frontal variant" of AD in which the frontal cortex is heavily affected by neurofibrillary tangles potentially early in the course of the disease (Taylor et al. 2008) and posterior cortical atrophy, where neurofibrillary tangles and plaques predominantly accumulate in the parietal and occipital cortices in most cases (Crutch et al. 2012). Typically, however, reduced volumes (Juottonen et al. 1998) and cortical thinning are observed in the PRc and ERc early in the course of disease (Dickerson et al. 2009), and these changes appear to be related to the accumulation of neurofibrillary tangles and consequent neuronal loss (Silbert et al. 2003). MTL atrophy is accompanied by a progressive episodic memory impairment characterized by poor learning and rapid forgetting, as well as semantic memory impairments (Taylor and Monsch 2007; Salmon and Bondi 2009; Salmon 2011). Cortical thinning throughout the neocortex can be observed at later stages of the disease (Lerch et al. 2005) and is associated with progressive impairments in other cognitive domains such as language and visuospatial processing.

The predicted exponential increase in the incidence of AD (Qiu et al. 2009) has refocused dementia research more strongly on identifying the earliest possible markers of neurofibrillary pathology. The discovery of early or "preclinical" markers would enable the initiation of therapies at a point in the disease process when they are expected to be maximally beneficial. One strand of research investigates the utility of fMRI imaging of memory functioning for the early detection of AD. These studies demonstrate that AD patients show decreased activation in the hippocampus during episodic memory tasks relative to controls (Rombouts et al. 2000; Machulda et al.

2003; for a review, see Dickerson and Sperling 2008). However, patients with aMCI, a putative prodromal stage of AD, tend to show the opposite effect, that is, increased MTL BOLD responses during memory tasks compared to normal control participants (Dickerson et al. 2004). In a similar vein, increased functional activity in the MTL was observed in healthy participants carrying one or two apoE ε4 alleles associated with an increased risk for AD (Bondi et al. 2005). Heightened MTL activity in preclinical stages and reduced MTL activity in early AD may reflect compensatory hyperactivation in the early stages of the disease and a breakdown of these compensatory mechanisms as the disease progresses (see, e.g., Dickerson et al. 2004). Thus, the development of preclinical BOLD markers of AD faces the challenging task of discriminating normal from pathologically enhanced or pathologically reduced levels of MTL activity, that is, of defining what "normal" BOLD responses during memory formation are.

A potentially fruitful approach to the identification of very early AD is to combine knowledge about the spatiotemporal sequence of neurofibrillary tangle formation and MTL functional specialization described above (Barbeau et al. 2004; Taylor and Probst 2008). Specifically, since the tau pathology associated with the cognitive dysfunction in AD typically begins in the PRc (Braak and Braak 1991), PRc dysfunction as revealed by neuropsychological testing may signal very early and still preclinical AD changes. Preliminary evidence from cross-sectional studies provides proof of this principle: crossmodal integration and complex perceptual and semantic analyses of individual objects, functions associated with the PRc (see above), are indeed impaired in individuals with amnestic MCI and early AD, and these impairments were shown to be related to the integrity of the PRc as estimated by voxel-based morphometry, cortical thickness, and fractional anisotropy MR measures (Hirni et al. 2011; Kivisaari et al. 2012; Taylor et al. 2011b). We note that the neuropsychological changes associated with PRc dysfunction may be subtle in nature, that is, not necessarily detectable in daily life (viz., episodic memory impairments), but demonstrable upon directed neuropsychological testing. Future interdisciplinary research combining neuropsychological and imaging with genetic and cerebrospinal fluid measures will undoubtedly reveal more specific and valid preclinical markers of AD which will be of great utility in the upcoming decades.

## 24.4 Anatomy of the MTL

The accurate identification of the MTL subregions is the prerequisite for understanding and studying their functional relevance. Further, we provide an overview of the gross anatomy of the MTL and a segmentation protocol for the reliable identification of these regions on anatomic MR scans. This parcellation scheme is based primarily on cytoarchitecture (Insausti et al. 1998; Suzuki and Amaral 2003a; Blaizot et al. 2010), myeloarchitecture (Hopf 1956), and patterns of white matter connectivity (Suzuki and Amaral 1994a; Saleem et al. 2007; Zilles and Amunts 2009).

### 24.4.1 Overview of the Gyral and Sulcal Characteristics of the MTL

The MTL region is characterized by three major gyri, the uncus (U, Fig. 24.1), the parahippocampal gyrus (PHg, Figs. 24.1 and 24.2), and the fusiform gyrus (Fg, Fig. 24.2), and two major sulci, the hippocampal fissure (Hf, Fig. 24.2), which is located superior to the parahippocampal gyrus, and the collateral sulcus (Cs, Figs. 24.1 and 24.2), which separates the parahippocampal gyrus from the fusiform gyrus (Fg, Fig. 24.2). Together, these gyral and sulcal landmarks are key to identifying the hippocampus proper, ERc, PRc, and PHc.

The uncus is the most medial and superior gyrus in the MTL, and its characteristic bulges are visible on a surface view (Fig. 24.1). From anterior to posterior sections, these bulges correspond to the gyrus ambiens (gA, Figs. 24.1 and 24.2; part of the ERc), the uncinate gyrus

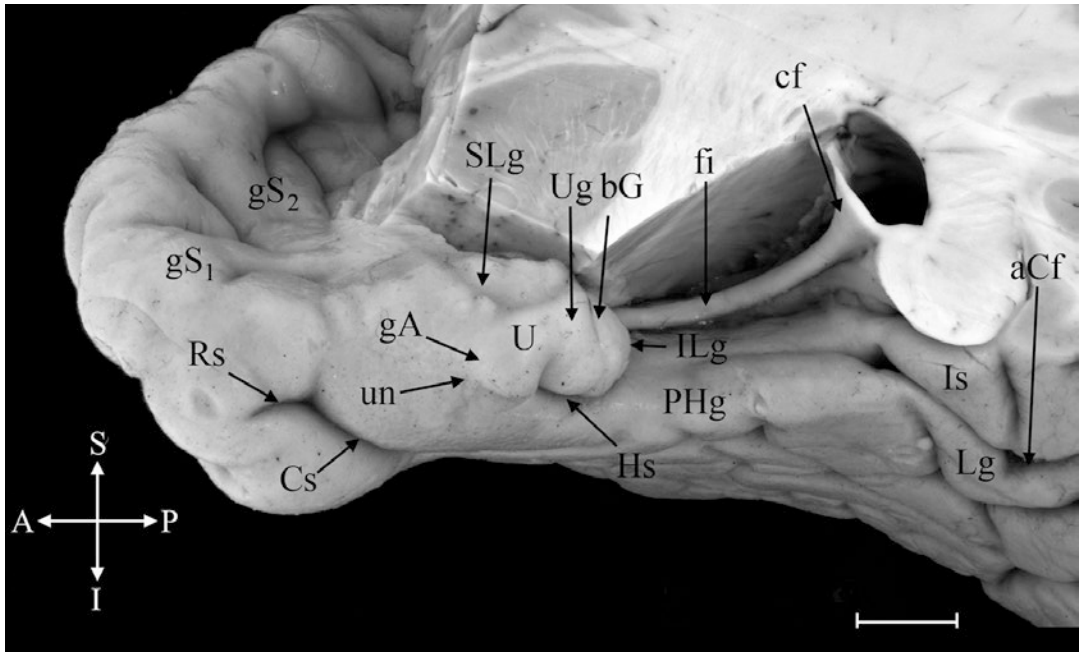


**Fig. 24.1** A superomedial view of the right MTL. *Abbreviations*: *aCf* anterior calcarine fissure, *bG* band of Giacomini, *Cs* collateral sulcus, *cf* crus of the fornix, *fi* fimbria, *gA* gyrus ambiens, *gS* gyrus of Schwalbe (this brain has two gyri of Schwalbe, indicated by subscripts), *Hs* hippocampal sulcus, *ILg* intralimbic gyrus, *Is* isthmus, *Lg* lingual gyrus, *PHg* parahippocampal gyrus, *Rs* rhinal sulcus, *SLg* semilunar gyrus, *U* uncus *Ug* uncinate gyrus, and *un* uncal notch. The temporal lobe is viewed from slightly oblique angle medially. Crosshairs indicate *S* superior, *A* anterior, *I* inferior, and *P* posterior. The bar represents circa 1 cm

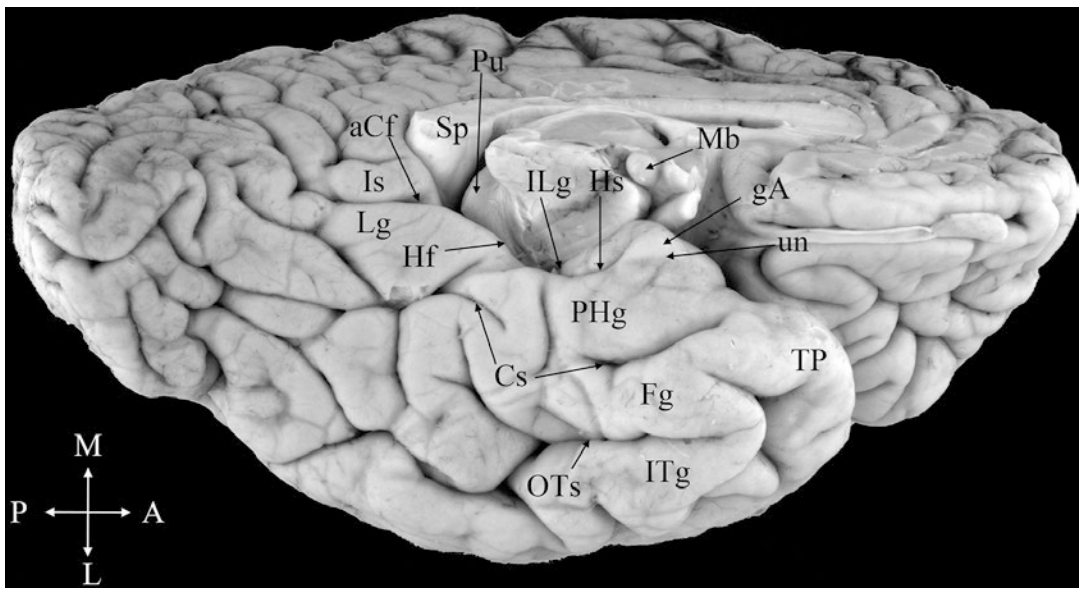


**Fig. 24.2** An inferior view of the left cerebral hemisphere. In this brain, the collateral sulcus has an interrupted trajectory. *Abbreviations*: *aCf* anterior calcarine fissure, *Cs* collateral sulcus, *Fg* fusiform gyrus, *gA* gyrus ambiens, *Hf* hippocampal fissure, *Hs* hippocampal sulcus, *ILg* intralimbic gyrus, *Is* isthmus, *ITg* inferotemporal gyrus, *Lg* lingual gyrus, *Mb* mamillary body, *OTs* occipitotemporal sulcus, *Pu* pulvinar, *PHg* parahippocampal gyrus, *Sp* splenium of the corpus callosum, *TP* temporal pole, and *un* uncal notch. The approximate anatomical directions are indicated by crosshairs (*M* medial, *A* anterior, *L* lateral, *P* posterior)

(Ug, Fig. 24.1), and the intralimbic gyrus (ILg, Figs. 24.1, 24.2, 24.6, and 24.7), where the band of Giacomini (bG, Fig. 24.1) separates the uncinate from the intralimbic gyrus. The posterior apex of the intralimbic gyrus represents an important anatomical landmark for the separation of the ERc/PRc from the PHc (see below). The uncal notch (un; Figs. 24.1 and 24.2) is an indentation formed mechanically by the free edge of the tentorium cerebelli (Van Hoesen et al. 2000). The parahippocampal gyrus containing most of the ERc, PRc, and PHc lies inferolateral to the uncus (PHg, Figs. 24.1 and 24.2). The parahippocampal gyrus is bordered inferolaterally by the fusiform gyrus. The temporal pole (TP, Fig. 24.2) represents the anterior extreme of the entire MTL, and it typically contains one or two gyri of Schwalbe on its superior surface (gS, Figs. 24.1 and 24.3).

The hippocampal sulcus (Hs, Fig. 24.1; also known as the uncal sulcus) separates the uncus from the adjacent parahippocampal gyrus (Insausti and Amaral 2004). It starts as a shallow sulcus and deepens progressively at more posterior levels. Posterior to the apex of the intralimbic gyrus, that is, after the uncus ends, the hippocampal sulcus continues as the hippocampal fissure (Fig. 24.2). At more lateral and anterior levels, the rhinal sulcus (Rs, Fig. 24.1) separates the parahippocampal gyrus from the temporal pole (Hanke 1997). The collateral sulcus replaces the rhinal sulcus at more posterior levels, where it separates the parahippocampal gyrus from the fusiform gyrus (Fig. 24.2). The rhinal and collateral sulci are anatomically variable across individuals, for example, the collateral sulcus may be deep or shallow, may bifurcate, or may be interrupted along its anterior-posterior extent. The occipitotemporal sulcus (OTs; Fig. 24.2) is the most lateral sulcus on the ventral surface of the temporal lobe (Fig. 24.2) and separates the fusiform gyrus from the inferior temporal gyrus (ITg, Fig. 24.2; Van Hoesen et al. 2000). At its most posterior levels, the parahippocampal gyrus is longitudinally divided into two gyri by the anterior calcarine fissure (aCf; Figs. 24.1, 24.2, and 24.9): the superior part forms the isthmus of the retrosplenial cortex (Is, Fig. 24.1), while the inferior part forms the lingual gyrus (Lg; Figs. 24.1 and 24.9).

### 24.4.2 A Segmentation Protocol for the MTL

A protocol for identifying the anatomical borders of the MTL substructures is described below. The protocol begins with the most anterior and lateral structure – the PRc – and continues medially to the ERc, posteriorly to the PHc before describing the most medial structure, the hippocampus proper. All landmarks are based on anatomical studies of the MTL in humans and nonhuman primates (e.g., von Economo and Koskinas 1925; Hopf 1956; Watson et al. 1992; Insausti et al. 1998; Pruessner et al. 2000, 2002; Malykhin et al. 2007; Taylor and Probst 2008) and were

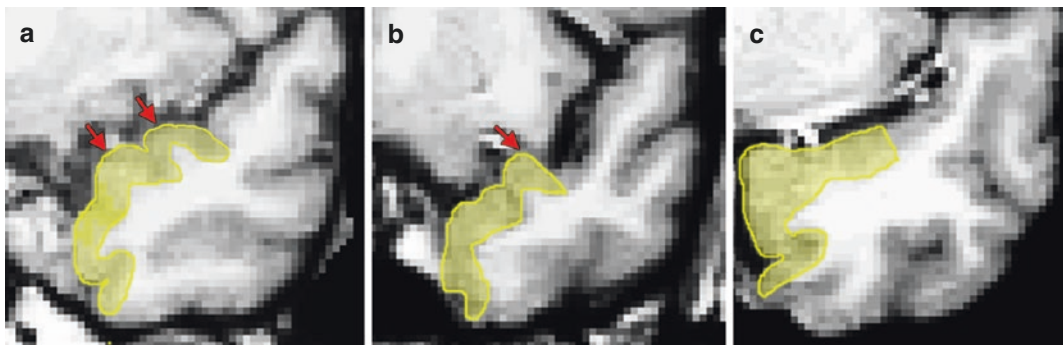


**Fig. 24.3** Native space coronal slices of the right hemisphere temporal pole area 1–2 mm anterior to the limen insulae. The figure illustrates the three variants of the gyri of Schwalbe (*red arrows*) and corresponding locations of the PRc (*yellow outlines*): (**a**) a case with two gyri of Schwalbe, (**b**) a case with one gyrus of Schwalbe, and (**c**) a case whose superior aspect of the temporal pole is relatively flat, indicating no gyri of Schwalbe

selected such that they can be readily identified on structural MR images. All landmarks refer to coronal views of volumes of 1 cubic mm resolution reoriented along the AC-PC axis and assume that the contrast is set to optimize the differentiation of gray from white matter.

#### 24.4.2.1 Borders of the Perirhinal Cortex

The PRc lies folded inside the collateral sulcus such that only a small part is visible from the cortical surface (Fig. 24.4). The PRc is bordered anteriorly by the temporal pole, posteriorly by the PHc, medially mainly by the ERc, and laterally by the fusiform gyrus. The medial portion of the PRc, that is, the TR, is a cytoarchitectonically distinct transition region between the PRc and ERc and notable as the site of incipient cortical neurofibrillary pathology in AD (Fig. 24.4; Braak and Braak 1985). The anteriorly situated temporal pole is a heterogenous cortex which shares some commonalities with the PRc (Suzuki and Amaral 2003a; Blaizot et al. 2010). According to some authors, the PRc extends into temporopolar cortex (Suzuki and Amaral 2003a; Insausti et al. 1998; Ding et al. 2009; but see also Brodmann 1909; von Bonin and Bailey 1947). However, since the precise extension of the PRc into the temporal pole and the corresponding anatomical borders are under debate (*cf.* Insausti et al. 1998; Ding et al. 2009; Ding and Van Hoesen 2010), the tempopolar cortex is excluded from this protocol.

The PRc is one of the most challenging structures to identify, in part because the boundaries of this structure have been redefined over time (Suzuki and Amaral 2003b) and because of the variability of its key anatomical landmark – the collateral sulcus (Hanke 1997; Pruessner et al. 2002). The medial and posterior PRc landmarks described below apply to the whole PRc including the TR, its medial extent. After a description of the anatomical borders of the PRc, the anatomical borders of the TR are defined. All landmarks take into account the dependence of the PRc and TR location on the shape and depth of the collateral sulcus (Insausti et al. 1998; Taylor and Probst 2008).

#### Perirhinal Cortex

##### Anterior Border

A cytoarchitectonic study of the human MTL demonstrated that the anterior portion of the

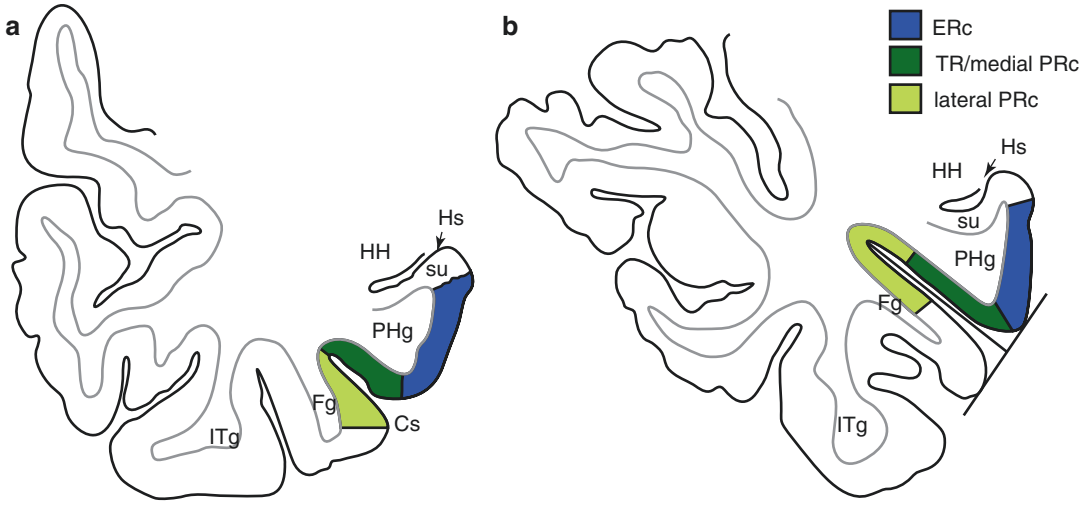


**Fig. 24.4** Coronal view of the medial temporal lobe at the level of the hippocampal sulcus (similar coronal level as Fig. 24.8). The locations of the PRc and TR depend on the depth of the collateral sulcus (*Cs*; see text): (**a**) borders when the collateral sulcus is of regular depth (i.e., 1–1.5 cm) and (**b**) when the collateral sulcus is deep (i.e., > 1.5 cm). Abbreviations: *Fg* fusiform gyrus, *HH* hippocampal head, *Hs* hippocampal sulcus, *ITg* inferotemporal gyrus, *PHg* parahippocampal gyrus, *su* subiculum of the hippocampus

PRc wraps around the anterior end of the ERc (Insausti et al. 1998). The anterior border of the PRc is located circa 24 mm posterior to the apex of the temporal pole or a few millimeters anterior to the most anterior appearance of gray matter of the limen insulae (i.e., frontotemporal junction; Fig. 24.8; Insausti et al. 1998). Since the length of the temporal pole is more variable than the appearance of the limen insulae gray matter, the anterior PRc border is defined as 2 mm anterior to the most anterior coronal slice containing gray matter in the limen insulae, which corresponds to approximately $y = 9$ in MNI coordinates (Fig. 24.8). The collateral sulcus is typically visible at this level. As noted above, the cytoarchitectonic similarities between the temporopolar region and the PRc indicate that this border may underestimate the true anterior extent of the PRc; however, the resolution of this issue requires additional research (see, e.g., Insausti et al. 1998; Suzuki and Amaral 2003b).

### Superolateral/Medial Border

At levels anterior to the limen insulae, the superolateral border is defined with respect to the number and position of the gyri of Schwalbe, which are considered part of the PRc (see Figs. 24.1, 24.3, and 24.8). In the presence of two gyri of Schwalbe, each laterally bordered by a temporopolar sulcus (prevalence ca. 80%; Insausti et al. 1998), the superolateral border is the fundus of the most lateral temporopolar sulcus (Figs. 24.3a and 24.8). When there is one gyrus of Schwalbe (prevalence ca. 12%; Insausti et al. 1998), the superolateral border of the PRc is defined as the fundus of the temporopolar sulcus (see Fig. 24.3b). If the gyrus of Schwalbe is not visible (prevalence ca. 8%; Insausti et al. 1998), the superolateral border is defined as the midpoint between the medial and lateral corners of the superior surface of the temporal pole (Fig. 24.3c; Insausti et al. 1998).

At the level of the gray matter of the limen insulae and posterior to this landmark, the medial border of the PRc is the shoulder of the medial bank of the collateral sulcus (Fig. 24.8; Insausti et al. 1998; Taylor and Probst 2008). This also serves as the medial border of the entire TR (see below). If the collateral sulcus is not yet present, or is discontinuous, the medial PRc border is estimated by approximating the angle of the trajectory of the shoulder of the medial bank of the collateral sulcus from more posterior slices.[5] If the collateral sulcus is bifurcated, the criteria described above are applied to the most medial sulcus (Taylor and Probst 2008). Posteriorly, the PRc wraps medially around the ERc and extends 2–4 mm posterior to the last slice containing the apex of the intralimbic gyrus (i.e., the posterior border of the ERc). At this level, the medial border of the PRc extends to the most medial aspect of the parahippocampal gyrus (*cf.* medial ERc border below).

### Lateral Border

The lateral border of the PRc depends on the length and shape of the collateral sulcus (Insausti et al. 1998). If the collateral sulcus is of regular depth between 1 and 1.5 cm deep (82% of cases; Insausti et al. 1998), the lateral boundary is the shoulder of the lateral bank of the collateral sulcus (Fig. 24.4a). If the collateral sulcus is shallow, that is, less than 1 cm deep (16% of cases; Insausti et al. 1998), the lateral border is the midpoint of the fusiform gyrus. We note that this criterion is not applied to the most anterior sections where the collateral sulcus begins to appear; in these anterior sections, the criteria for the regular collateral sulcus are applied or the border is estimated from more posterior slices with an obvious collateral sulcus (*cf.* (Insausti et al. 1998), Fig. 24.5). Finally, if the collateral sulcus is deeper than 1.5 cm (2% of cases), the lateral border is the midpoint between the fundus and the shoulder of the lateral bank of the collateral sulcus (Fig. 24.4b).

### Posterior Border

As in its anterior aspect, the PRc wraps around the posterior end of the ERc forming a border averaging 3 mm wide (range, 2–4 mm; Insausti et al. 1998; see also Krimer et al. 1997). The

[5]The protocol assumes that in cases where the collateral sulcus cannot be visualized or is discontinuous, the lateral and medial PRc borders are determined on coronal slices anterior and posterior to the interrupted section, and that imaginary lines are drawn from these anterior and posterior levels to connect the lateral borders and the medial borders of the PRc.

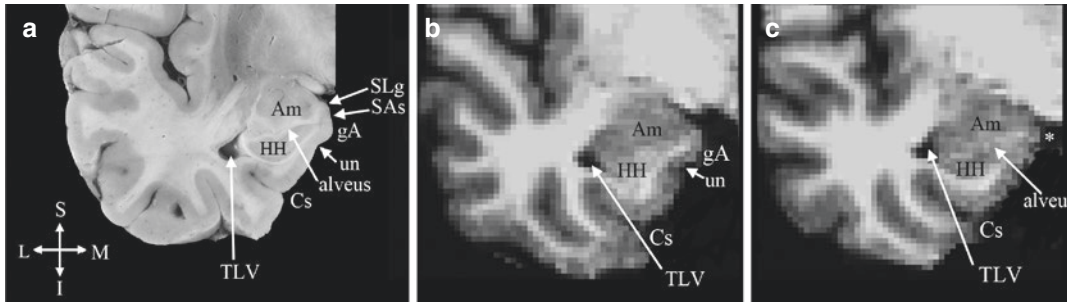


**Fig. 24.5** Sections of the temporal lobe at the level of the uncus (approximate MNI $y = -5$): (**a**) a histological section and (**b**) an MRI slice at a similar coronal level where the gyrus ambiens (*gA*) and uncal notch (*un*) are visible. (**c**) An MRI slice at a similar coronal level where the gA and un are not visible. In these instances, the medial apex of the parahippocampal gyrus (*asterisk*) is defined as the medial ERc border. Abbreviations: *Am* amygdala, *Cs* collateral sulcus, *gA* gyrus ambiens, *HH* hippocampal head, *SAs* semiannular sulcus, *SLg* semilunar gyrus and *TLV* temporal horn of the lateral ventricle, *un* uncal notch. Anatomical directions: *S* superior, *M* medial, *I* inferior, *L* lateral

posterior border is therefore set at 3 mm posterior to the last coronal slice still containing the apex of the intralimbic gyrus, that is, the posterior border of the ERc (e.g., if the last coronal slice containing the intralimbic gyrus is MNI $y = -18$, the last posterior slice with the PRc is MNI $y = -21$, see Fig. 24.8).

### Transentorhinal Area

#### Anterior Border

The medial aspect of the PRc, the TR, is defined as an area of transition between the ERc and PRc (Braak and Braak 1985). Therefore, its anterior border is defined as the first slice where the ERc is present, that is, 2 mm posterior to the first anterior slice where the white matter of the limen insulae is visible (Fig. 24.8; see Sect. 19.4.2.2).

#### Medial Border

The medial border of the TR is identical to the medial border of the PRc described above, that is, the shoulder of the medial bank of the collateral sulcus (Insausti et al. 1998; Taylor and Probst 2008; Fig. 24.4 and 24.8.

#### Lateral Border

If the depth of the collateral sulcus equals or is less than 1.5 cm, the lateral border of the TR is defined as the fundus of the collateral sulcus (Fig. 24.4a; Taylor and Probst 2008). If the collateral sulcus is deeper than 1.5 cm, the lateral border is the midpoint between (i) the shoulder of the medial bank of the collateral sulcus and (ii) the midpoint of the lateral bank of the collateral sulcus (Fig. 24.4b; Insausti et al. 1998; Taylor and Probst 2008). If the collateral sulcus is bifurcated, these criteria are applied to the most medial sulcus (Taylor and Probst 2008).

#### Posterior Border

The posterior border of the TR is identical to the posterior border of the ERc, that is, 1 mm posterior to the last slice containing the apex of the intralimbic gyrus (see below).

### 24.4.2.2 Borders of the Entorhinal Cortex

The ERc is the largest cortical field on the parahippocampal gyrus and is entirely visible from the medial surface view. Macroscopically, the anterior portion of the ERc is characterized by small bumps on the cortical surface called *verrucae hippocampi* (Klingler 1948). The ERc encompasses the gyrus ambiens at anterior levels (Figs. 24.1, 24.2, 24.5, and 24.8). The gyrus ambiens is superomedially neighbored by the semiannular sulcus, beyond which lies the semilunar gyrus of the periamygdaloid cortex. At more posterior levels, the subiculum of the hippocampus proper neighbors the ERc superomedially. The PRc surrounds the anterior, inferior, and lateral sides of the ERc (Insausti et al. 1998).

#### Anterior Border

Cytoarchitectonic studies have demonstrated that the PRc surrounds the anterior end of the ERc (Insausti et al. 1998). However, because the oblique orientation of the anterior end of the ERc is difficult to delineate, a conservative anterior border is defined corresponding to the most anterior coronal slice with the full extent of the ERc (but see Insausti et al. 1998). This level corresponds approximately to a coronal slice 2 mm posterior to the first anterior slice where the white matter of the limen insulae is visible. Note that because of this conservative border, a segment of the MTL is left uncategorized (Fig. 24.8).

#### Medial Border

At anterior levels, the medial border of the ERc is the semiannular sulcus (Fig. 24.5). However, because this sulcus is very shallow and seldom identifiable on MR images, the medial border of the anterior ERc is defined here as the midpoint (i.e., medial apex) of the gyrus ambiens (Figs. 24.5b, 24.8). If the gyrus ambiens is not visible, the medial border is the shoulder (i.e., medial apex) of the superomedial bank of the parahippocampal gyrus (see Fig. 24.5c, 24.8). The medial ERc border moves slightly inferiorly when the hippocampal sulcus emerges (Fig. 24.8). However, because this transition is difficult to detect on MR images, an arbitrary landmark is defined as 1 mm anterior to first anterior slice where the hippocampal sulcus can be visualized (see Fig. 24.8). At this and more posterior levels, the most medial extent of the parahippocampal gyrus, that is, its medial apex, is the medial border of the ERc.

#### Lateral Border

The lateral border of the ERc is identical to the medial border of the PRc/TR (see above and Figs. 24.4 and 24.8; Taylor and Probst 2008; Krimer et al. 1997).

#### Posterior Border

The posterior border of the ERc is defined as 1 mm posterior to the last slice containing the apex of the intralimbic gyrus (Fig. 24.6; note that the apex is located in between slices Fig. 24.8, $y = -18$, which is not shown).

### 24.4.2.3 Borders of the Parahippocampal Cortex

The PHc is located in the posterior portion of the parahippocampal gyrus posterior to the PRc and ERc (Van Hoesen 1982; Sewards 2011). However, disagreement exists regarding the precise cytoarchitectonic features of the PHc, and correspondingly, the anatomical boundaries of the PHc are inconsistently defined in the literature (see, e.g., von Economo and Koskinas 1925; Hopf 1956; Saleem et al. 2007; Thangavel et al. 2008). Here, we draw upon the conceptualizations of the PHc as a proisocortical region, that is, a transitional zone between allocortex and neocortex, and as the posterior continuation of the PRc and ERc

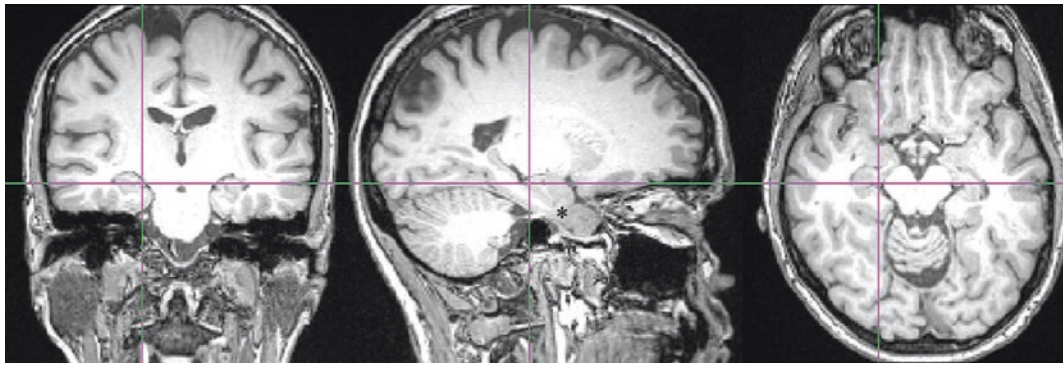

**Fig. 24.6** Coronal, sagittal, and axial views of one participant with the crosshair position indicating the location of the apex of the intralimbic gyrus. The *asterisk* in the sagittal view indicates the cone-shaped crossing of the alveus and parahippocampal gyrus white matter, which marks the anterior limit of the hippocampal head

(Suzuki and Amaral 2003a; Saleem et al. 2007). Thus, the definition of the lateral border of the PHc described below is consistent with Hopf (1956; see also Sewards 2011) and corresponds closely to anatomical descriptions in nonhuman primates (Suzuki and Amaral 2003a; Saleem et al. 2007).

As noted above, the PHc is defined as the posterior continuation of the PRc and ERc, located inferolateral to the subiculum of the hippocampal body and tail. Posteriorly, the anterior calcarine fissure divides the PHc longitudinally into the inferiorly situated lingual gyrus and the superiorly situated isthmus of the retrosplenial cortex (Figs. 24.1, 24.2, and 24.9). The PHc occupies parts of the lingual gyrus and merges without clear anatomical landmarks with the infra- and retrosplenial cortices (Vogt et al. 2006). For this reason, the posterior limit of the PHc is conservatively restricted to levels anterior to the emergence of the calcarine fissure.

#### Anterior Border

The anterior boundary of the PHc is defined as the first slice after the posterior border of PRc, that is, 4 mm posterior to the last slice containing the apex of the intralimbic gyrus (Fig. 24.9).

#### Medial Border

The subiculum of the hippocampus proper neighbors the PHc medially (*cf*. Figure 24.4). Thus, the medial border is the medial apex of the parahippocampal gyrus (Fig. 24.9).

#### Lateral Border

According to studies on nonhuman primates (Suzuki and Amaral 2003a; Saleem et al. 2007) and the myeloarchitectonic study by Hopf (1956; see Sewards 2011), the PHc represents the posterior extension of the PRc and ERc (but see von Economo and Koskinas 1925). Thus, the lateral border of the PHc is adjusted according to the depth of the collateral sulcus in the same manner as for the lateral border of the PRc (see Section "Perirhinal Cortex"; Figs. 24.4 and 24.9).

#### Posterior Border

The posterior end of the PHc is funnel-shaped and progressively merges with the retrosplenial region. According to Vogt et al. (2006), the PHc extends posteriorly several millimeters past the posterior limit of the splenium. However, because the medial and lateral PHc borders at these posterior levels are unclear, a conservative posterior border is defined as the first posterior slice where the pulvinar is no longer visible (Figs. 24.2 and 24.9). Anterior to this level, the lateral and medial landmarks described above can be used.

### 24.4.2.4 Borders of the Hippocampus Proper

This chapter focuses on the retrocommissural part of the hippocampus proper, extending from the inferior and medial side of the amygdala at the uncinate gyrus to an area posterior and inferior to the splenium of the corpus callosum (Fig. 24.7). This part of the hippocampus is entirely situated inferior to the corpus callosum and appears as a C-shaped structure when viewed from above (Fig. 24.7). Posterior to the apex of the uncus, the hippocampus proper arches laterally around the upper midbrain and curves medially and superiorly, continuing as a thin strip of gray matter of vestigial hippocampus (*indusium griseum*) on the superior surface of the corpus callosum (supracommissural hippocampus) before descending at anterior levels to the subcallosal area (precommissural hippocampus). The supra- and precommissural hippocampi are excluded from this segmentation. The alveus is made of the fibers emanating from the pyramidal cells of the hippocampus. It covers the Ammon's horn superiorly and laterally (Fig. 24.5), and its fibers converge to form the fimbria, oriented roughly along the longitudinal axis of the hippocampus (Duvernoy 1998). The fimbria is continuous with a prominent, flattened white matter tract, the crus of the fornix (Figs. 24.1 and 24.9), which begins at posterior levels of the hippocampus and curves superomedially below the corpus callosum. These white matter tracts likewise are excluded from the segmentation (Hogan et al. 2000; Pantel et al. 2000, but see also Pruessner et al. 2000; Malykhin et al. 2007).

Because different anterior to posterior areas of the hippocampus exhibit different patterns of connectivity (Witter and Amaral 1991), which presumably corresponds to functional specializa-

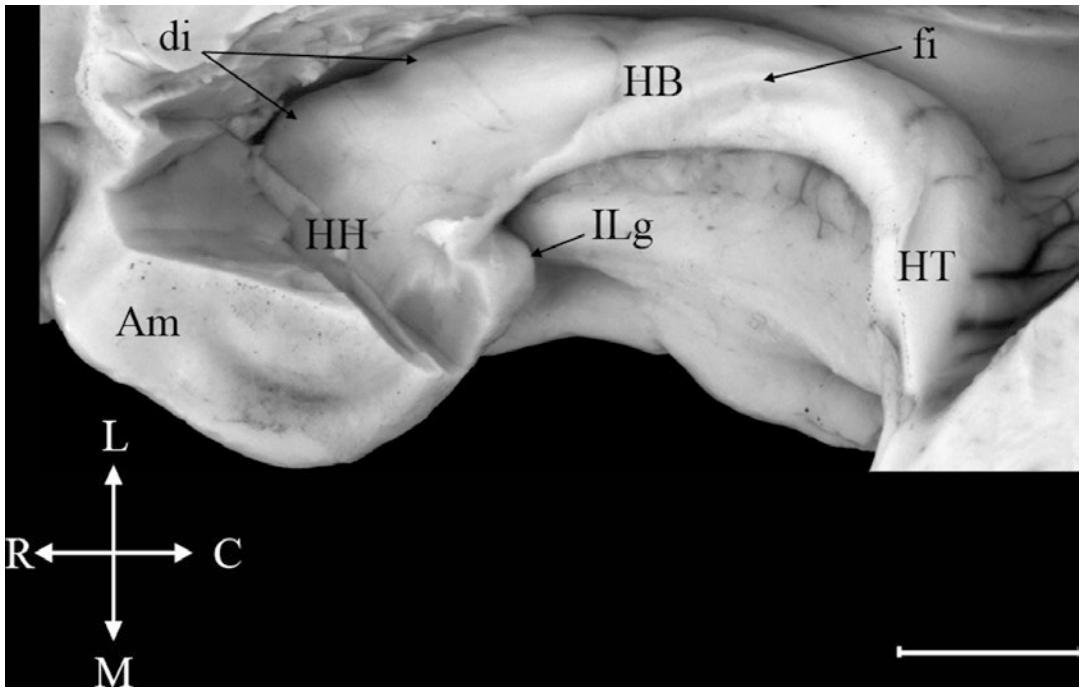


**Fig. 24.7** Superior view of the C-shaped hippocampal formation on the right hemisphere after removing the roof of the temporal horn and parts of the amygdala. This view thereby reveals the intra- and extraventricular aspects of the hippocampal formation. Abbreviations: *Am* amygdala, *di* hippocampal digitations, *fi* fimbria, *HB* hippocampal body, *HH* hippocampal head, *HT* hippocampal tail, and *ILg* intralimbic gyrus. *Anatomical directions*: *L* lateral, *P* posterior, *M* medial, and *A* anterior. The bar represents circa 1 cm

tion along its longitudinal axis (see Sect. 19.2; Colombo et al. 1998; Moser and Moser 1998; Giovanello et al. 2004), we describe anatomical landmarks for the hippocampal head, body, and tail separately (see also Watson et al. 1992; Pantel et al. 2000; Pruessner et al. 2000; Maller et al. 2006; Malykhin et al. 2007). Anatomical tracing typically starts at the anterior border of the hippocampal body and continues to the posterior end of the hippocampal tail. The most anterior aspect, the hippocampal head, lies adjacent to the amygdala and is the most challenging hippocampal structure to trace. This protocol, therefore, starts with the body of the hippocampus and then discusses the tail and finally the head of the hippocampus.

## Hippocampal Body

The hippocampal body consists of subfields CA1–3 and the subiculum which is located on the superior bank of the parahippocampal gyrus. The fimbria is located on the superomedial side of the hippocampus and has a slightly curved trajectory toward the hippocampal tail, where it leaves the hippocampus and continues its path superomedially as the crus of the fornix (Fig. 24.1). For a graphical illustration of the segmentation of the hippocampal body, see Figs. 24.8 and 24.9.

### Anterior Border

The anterior border of the hippocampal body is defined as one slice posterior to the posterior apex of the intralimbic gyrus (i.e., the last slice containing the intralimbic gyrus; Fig. 24.8; Malykhin et al. 2007).

### Medial Border

The subiculum of the hippocampus proper extends to the medial apex of the parahippocampal gyrus, which represents the medial border of the hippocampus proper (Figs. 24.8 and 24.9; Watson et al. 1992).

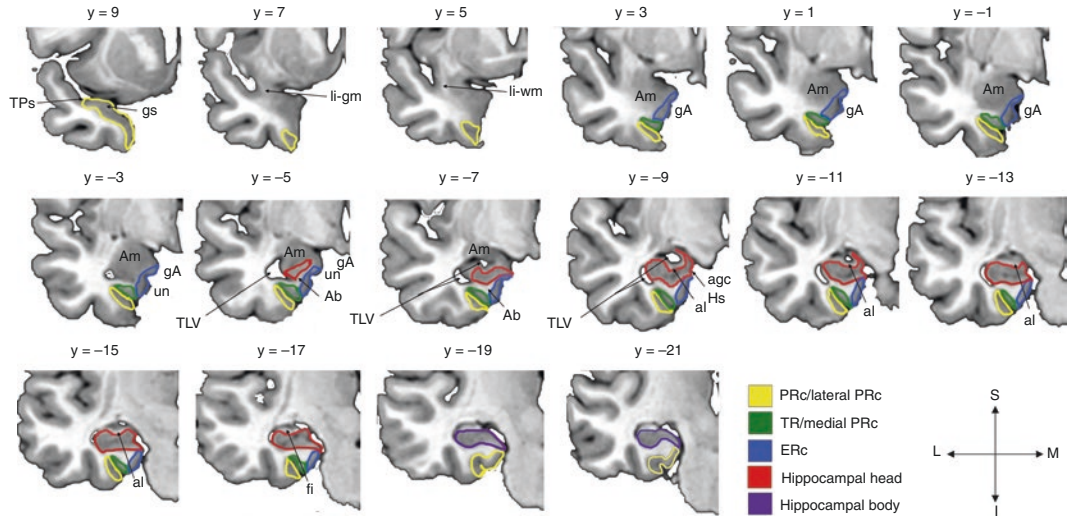


**Fig. 24.8** Coronal sections of the temporal lobe at anterior to posterior levels every 2 mm. The coronal level is identified in MNI coordinates. The asterisk represents the most anterior slice where the TLV is continuous with the quadrigeminal cistern (i.e., where ventricular slit is present). The structures are drawn on an MriCron template (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Note that a part of the medical surface is unsegmented due to the unreliability of tracing the oblique anterior end of the ERc (see text). The fimbria begins only at the level of posterior hippocampal head. *Abbreviations*: *Ab* angular bundle (parahippocampal gyrus white matter), *al* alveus, *Am* amygdala, *fi* fimbria, *gA* gyrus ambiens, *Hs* hippocampal sulcus, *ILg* intralimbic gyrus (the apex is located at $y = -18$), *qgc* quadrigeminal cistern, li-*gm* limen insulae gray matter, *li-wm* limen insulae white matter, *TLV* temporal horn of the lateral ventricle, and *un* uncal notch. Anatomical directions: *S* superior, *M* medial, *I* inferior, and *L* lateral

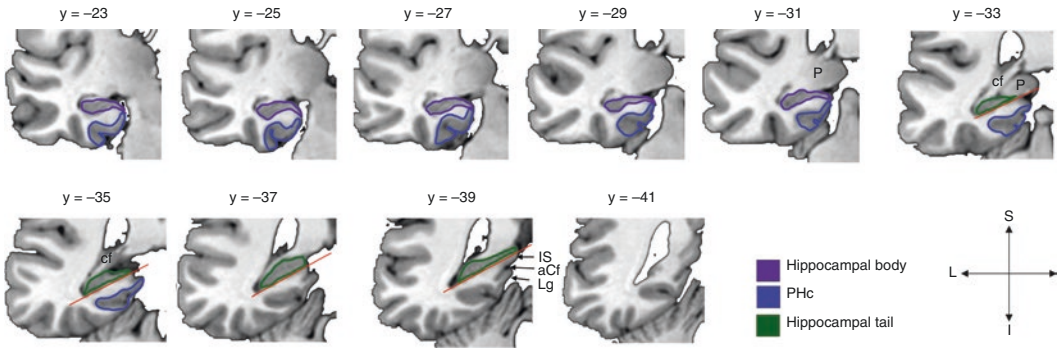


**Fig. 24.9** Coronal sections of the temporal lobe at anterior to posterior levels every 2 mm. The numbers represent different coronal levels in MNI (*y*) coordinates. The structures are drawn on an MriCron template (http://www.mccauslandcenter.sc.edu/mricro/mricron/). The red line illustrates the arbitrary border used as the inferomedial limit of the hippocampal tail. *Abbreviations*: *aCf* anterior calcarine fissure, *cf* crus of the fornix, *Is* isthmus, *Lg* lingual gyrus, and *P* pulvinar. Anatomical directions: *S* superior, *M* medial, *I* inferior, and *L* lateral

### Lateral Border

The body of the hippocampus extends laterally to the temporal horn of the lateral ventricle (Figs. 24.8 and 24.9; Pantel et al. 2000; Pruessner et al. 2000; Malykhin et al. 2007).

### Inferior Border

Inferiorly and inferomedially, the body of the hippocampus is bordered by the white matter of the angular bundle of the parahippocampal gyrus (Figs. 24.8 and 24.9; Pantel et al. 2000; Malykhin et al. 2007).

#### Superior Border

The temporal horn of the lateral ventricle forms the superior boundary of the hippocampal body. Care should be taken to exclude the white matter of the fimbria (Hogan et al. 2000; Pantel et al. 2000 but see also Pruessner et al. 2000; Malykhin et al. 2007). Sagittal views may aid the visualization of the continuous border between the hippocampus proper and the cerebrospinal fluid of the lateral ventricle. Care must also be taken to exclude the voluminous choroid plexus, which fills the temporal horn of the lateral ventricle on the superior aspect of the hippocampus.

#### Posterior Border

The posterior border of the body of the hippocampus is one slice posterior to the first coronal slice where the crus of the fornix is clearly separated from the wall of the lateral ventricle or where its full profile is visible in columnar form, even if it is still attached to the lateral ventricle (Fig. 24.9; Maller et al. 2006; Malykhin et al. 2007).

### Hippocampal Tail

The tail of the hippocampus proper funnels slightly and turns medially before steeply ascending around the splenium of the corpus callosum (Fig. 24.7). The CA1 subfield occupies a progressively more medial position and forms the gyrus of Andreas Retzius on the surface of the parahippocampal gyrus, while the CA3 subfield forms the gyrus fasciolaris on the superior aspect of the hippocampal fissure (Duvernoy 1998). The location of the hippocampal tail is illustrated in Fig. 24.9.

#### Anterior Border

The anterior border of the hippocampal tail is defined as the first slice posterior to the posterior limit of the hippocampal body (Fig. 24.9; Maller et al. 2006; Malykhin et al. 2007).

#### Medial Border

The isthmus is located on the medial aspect of the hippocampus in an area which had been occupied by the subiculum at more anterior levels (Fig. 24.9). To ensure the exclusion of the isthmus, an arbitrary medial border for the hippocampal tail is defined: an oblique, straight line drawn from the inside inferolateral corner of the angular bundle along the white matter of the parahippocampal gyrus to the quadrigeminal cistern (see Fig. 24.9). The hippocampal tail is defined as the gray matter superolateral to this line.

#### Lateral Border

The lateral border of the hippocampal tail is the white matter of the ascending crus of the fornix and the temporal horn of the lateral ventricle (Fig. 24.9; Pantel et al. 2000; Maller et al. 2006).

#### Superior Border

The tail of the hippocampus proper is superiorly bordered by the crus of the fornix and the white matter of the splenium of the corpus callosum (Fig. 24.9). The pulvinar should be carefully avoided; toward this end, the sagittal plane is helpful in distinguishing the gray matter of the hippocampal tail from the gray matter of the thalamus (Pantel et al. 2000; Malykhin et al. 2007).

#### Inferior Border

The inferior border is the white matter of the parahippocampal gyrus (Pantel et al. 2000; Malykhin et al. 2007).

#### Posterior Border

The posterior portion of the hippocampal tail appears as an ovoid-shaped mass of gray matter (Fig. 24.9). The complete disappearance of this shape marks the posterior limit of the hippocampal formation (Fig. 24.9).

### Hippocampal Head

The hippocampal head (CA1–3, dentate gyrus, subiculum) abutting the temporal horn of the lateral ventricle bends medially and again posteriorly to become part of the uncus (Insausti and Amaral 2004). Anteriorly, the head of the hippocampus is located inferior to the amygdala (Fig. 24.7), which occupies a progressively larger superolateral area of the hippocampal-amygdaloid complex at more anterior levels (Fig. 24.8). Segmentation begins at posterior levels.

#### Posterior Border

The posterior border of the hippocampal head is the apex of the intralimbic gyrus, that is, the last slice containing this structure (Figs. 24.6 and 24.8; Duvernoy 1998; Malykhin et al. 2007).

This point may best be identified by navigating through sagittal slices.

#### Medial Border

At posterior levels, the hippocampal head is segmented up to the most medial apex of the parahippocampal gyrus (Fig. 24.8), whereas at anterior levels, the medial border is limited by the white matter of the parahippocampal gyrus (Fig. 24.8). The transition between the two landmarks takes place one slice anterior to the most anterior slice where the uncal sulcus is last visible, corresponding approximately to the level where the semilunar gyrus and anterior cortical nucleus of the amygdala appear.

#### Lateral Border

The lateral border is the medial wall of the temporal horn of the lateral ventricle (Pantel et al. 2000; Pruessner et al. 2000). If the white matter of the alveus is visible next to the wall of the lateral ventricle, it is excluded (Hogan et al. 2000; Pantel et al. 2000).

#### Superior Border

At posterior levels, the superior border can be identified as the temporal horn of the lateral ventricle or the white matter of the alveus if visible (Fig. 24.8). At more anterior levels where the amygdala is no longer separated from the hippocampus by a ventricular slit (transition approximately at Fig. 24.8), the hippocampus is delimited from the amygdala using the white matter of the alveus surrounding the superior aspect of the hippocampal head (Watson et al. 1992). If the alveus is not visible, especially at the most anterior levels, the location of the alveus and thus superior border is estimated from sagittal slices, where the alveus is usually easier to identify. The uncal recess of the inferior horn of the lateral ventricle may additionally aid delineation of the superomedial border of the hippocampal head (Watson et al. 1992; Hogan et al. 2000; Pruessner et al. 2000).

#### Inferior Border

The hippocampal head is inferiorly bordered by the white matter of the parahippocampal gyrus (Malykhin et al. 2007; Pruessner et al. 2000).

#### Anterior Border

The anterior border is defined as the most anterior corner of the conical profile formed by the parahippocampal gyrus white matter and the alveus, as visualized on sagittal views (see Fig. 24.6; Pantel et al. 2000; Pruessner et al. 2000). When this point is selected on the sagittal slice, the view is changed to coronal, where the medial, lateral, superior, and inferior borders can be identified.

## 24.5 fMRI in Alzheimer's Disease

Several techniques have been used to study AD-related disruptions of brain function. These include fMRI during cognitive tasks and during rest. Studies focusing on task-related activity in AD have found patterns of relative BOLD activation and deactivation depending on disease stage and the specific task used (e.g., Bondi et al. 2005; Gould et al. 2006; Rémy et al. 2005; Rombouts et al. 2005). However, the use of task-related fMRI may be impractical in the context of AD, particularly in clinical settings. The data may be difficult to obtain as the tasks more often than not require a significant amount of effort from the participant. The interpretation of these data may also prove challenging as patients with AD pathology may differ considerably in the levels of cognitive performance and the ability to sustain attention. In comparison, resting-state measurements do not require the participant to engage in a task, and they are, therefore, less strenuous for the patient. The interpretation of data may also be more straightforward as individual levels of task performance do not need to be taken into account.

Resting-state fMRI is based on fluctuations of spontaneous metabolic activity during rest, and it is most often used to test functional coupling or connectivity of different brain regions (for reviews, see Dennis and Thompson 2014; Liu et al. 2008). Several studies have reported decreases in hippocampal connectivity during rest in subjects with AD-related pathology (e.g., Allen et al. 2007; Wang et al. 2006). Specifically, AD has been shown to be associated with reduced hippocampal connectivity with multiple areas in the brain, including the medial prefrontal cortex and anterior cingulate cortex. These regions are

associated with episodic memory and may, therefore, play a role in the memory dysfunction in AD.

Independent component analysis has revealed disruptions in resting-state networks in AD. Most prominently, AD is associated with reductions in the default mode network connectivity, particularly in the hippocampus and posterior cingulate (Agosta et al. 2012; Binnewijzend et al. 2012; Damoiseaux et al. 2012; Greicius et al. 2004; Petrella et al. 2011). Several authors have also found increases particularly in the prefrontal cortex resting-state connectivity (Agosta et al. 2012; Supekar et al. 2008; Wang et al. 2006). In one study, the connectivity in the executive network in AD was associated with performance in tasks of executive functioning and language (Agosta et al. 2012) with increase in activity associated with better cognitive score. Therefore, the authors interpreted the findings as reflecting a compensatory mechanism in response to the pathological changes taking place in the brain.

The studies indicate that there are typical patterns of fMRI resting-state connectivity in AD. In the future, these measures may help in the detection of AD and may predict the conversion of AD longitudinally. However, to date, these measures have not been shown to be better predictors of AD pathology than cognitive scores (Petrella et al. 2011).

## 24.6 Summary

This chapter skimmed the surface of research on the functional neuroanatomy of the MTL. The most influential model of MTL functioning today emphasizes the role of the entire MTL in the formation of conscious memories. This view is supported by numerous patient findings as well as the dense interconnectivity within the MTL, enabling the subregions to work in concert, acting as a unified region. Animal and more recently human neuroscientific research, using ever more sophisticated methods and neuropsychological paradigms, indicates additional levels of processing in the MTL beyond declarative memory formation. Hierarchical, connectivity-based approaches provide a framework within which to study these multidimensional aspects of cognitive functioning in which each MTL subregion is also functionally specialized for a particular kind of information processing. This work not only furthers our basic understanding of the functional neuroanatomy of this complex system but also has obvious clinical implications for patients with acquired brain damage and neurodegenerative disorders, most notably AD. Thus, concerted activity among all MTL structures appears to take place in parallel with functionally specialized processing in each substructure, enabling successful memory encoding and retrieval of complex events, concepts, and scenes.

The prerequisite for advancements in MTL research is the use of well-defined and reliable anatomic landmarks, such as those reported in this chapter. Moreover, the use of different methodologies, tasks, and populations is essential to increase our understanding of human MTL function. Case or patient studies remain a cornerstone in MTL research, providing valuable information about the functions that are lost as a consequence of different kinds and locations of brain damage (e.g., Squire and Wixted 2011). However, this approach is limited by the fact that lesions typically encompass more than one cytoarchitectonic area, that is, that selective lesions of PRc, ERc, or PHc are rare. Thus, voxel-based volumetric methods (e.g., Tyler et al. 2005; Ashburner 2007) and surface-based methods offer increasingly reliable anatomical precision in patient studies (Dale et al. 1999; Fischl et al. 1999; Klein et al. 2010; Kivisaari et al. 2012). FMRI in healthy individuals, in particular, high-resolution imaging, has become increasingly important as it provides high spatial information on the systems normally engaged during a particular task (e.g., Henson 2005), although it does not provide information about whether the activated regions are *necessary* for the particular function. Finally, resting-state fMRI and diffusion-tensor imaging, among others, can increase our knowledge about the functional and structural connectivity of these areas in vivo, respectively, which is fundamental to our understanding of how the MTL areas work as a network and interact with other brain areas (e.g., Wang et al. 2006; Catani and Thiebaut de Schotten 2008). Converging evidence from diverse neuroscientific approaches using valid anatomic guidelines is expected to significantly increase our functional-neuroanatomic understanding of the MTL.

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