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What, if anything, is the medial temporal lobe, and how can the amygdala be part of it if there is no such thing?

Elisabeth A. Murray[a,*] and Steven P. Wise[b]

[a] *Laboratory of Neuropsychology, National Institute of Mental Health, Building 49, Room 1B80, MSC 4415, 49 Convent Drive, Bethesda, MD 20892-4415, USA*

[b] *Laboratory of Systems Neuroscience, National Institute of Mental Health, Building 49, Room B1EE17, MSC 4401, 49 Convent Drive, Bethesda, MD 20892-4401, USA*

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Abstract

Should the medial temporal lobe (MTL) of primates—which includes allocortical structures such as the hippocampus, neocortical structures such as the parahippocampal cortex, and nuclear structures such as the basolateral amygdala—be considered a single "thing"? According to the prevailing view, here termed the *reification theory*, the answer is yes. According to this theory, the MTL functions as an amalgamated entity that provides the neuronal mechanisms for declarative memory; the greater the damage to the MTL or any of its components, the greater the deleterious effects on declarative memory. A countervailing view, here called the *balkanization theory*, holds that the various components of the MTL process and store different kinds of information. According to this theory, damage to each part of the MTL causes a unique set of behavioral deficits—some involving memory, others involving perception, and yet others involving response selection. The empirical neuropsychological evidence favors the balkanization theory, as do some new concepts in theoretical neuroanatomy.
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1. Introduction

The questions posed in our title are admittedly ambiguous and somewhat strange, but they follow Swanson and Petrovich (1998) who asked: "What is the amygdala?" They answered that the amygdala is not any "thing," at all. Instead, they described the amygdala as a composite of other things, namely parts of the cortex, striatum, and claustrum. Our title also pays homage to the 1957 classic by Wood, "What, if anything, is a rabbit?" He explored a question posed early in the 20th century: Are rabbits a separate thing—in contemporary terms, a clade—or, as some experts thought at the time, various kinds of rodent? We, too, explore ideas about "things" that date to the early 20th century. We ask whether the medial temporal lobe (MTL) might be better understood if we imagined that there is no such thing. Of course, the structures in the MTL will not disappear as a result; they will continue to be where they are and do what they do. We hope, however, that it will prove helpful to change the question from "What does the MTL do?", which seems to assume a solitary answer, to the questions posed in our title, which recognize the structural diversity of the MTL.

To anticipate our presentation, we offer two take-home messages. First, according to a new view of forebrain organization, most parts of the MTL—including the hippocampus and much of the amygdala—function in recurrent, neural loops that include striatal and pallidal structures. In this context, theories that seek to contrast the functions of one entity called the MTL with other entities called "the striatum," "the basal ganglia," or "the corticostriatal system" need fundamental reconsideration or, at the very least, reformulation. Second, the MTL is not a "thing" at all, but a diverse collection of structures, each with its own embryological

* Corresponding author. Fax: 1-301-402-0046.
E-mail address: eam@ln.nimh.nih.gov (E.A. Murray).

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and evolutionary history. Each part of the MTL contributes to perception, memory, and response selection in its own way. This conclusion stands in stark contrast with the prevailing view of the MTL, which holds that "it" functions as an amalgamated declarative memory system. We begin with a brief survey of the prevailing view and its history.

2. The reification theory

The prevailing view of MTL function began to take shape roughly 50 years ago, when a patient—famously designated H.M.—underwent a bilateral excision of large parts of his MTL. As intended, the operation lessened the frequency and severity of his epileptic seizures. As one unintended side effect of the operation, however, H.M. became profoundly amnesic. Another unintended consequence of that surgery was five decades of neuropsychological research, which led to the prevailing view of the MTL and its functions, called here the *reification theory*.

The reification theory holds that the MTL is a single "thing," one that performs a unitary function as a declarative memory system. For example, Zola-Morgan, Squire, and Ramus (1994, p. 493) concluded that

> The severity of memory impairment increases as additional components of the medial temporal lobe memory system are damaged.

As one measure of declarative memory in monkeys, they evaluated performance on the delayed nonmatching-to-sample task (DNMS). In this task, each trial comprises two parts: a sample presentation and a choice test. In a typical DNMS experiment, monkeys first see and displace a single object, called the sample, to obtain a food reward hidden underneath. On the second part of the trial, monkeys are presented with two objects, the sample and a novel object, and they must choose the novel object to earn another food reward. Memory for the sample object is taxed by increasing the delay interval between the sample presentation and choice test. In the view of Zola, Squire, and their colleagues, damage to almost any part of the MTL leads to an impairment in the ability to learn the DNMS rule and to perform the DNMS task over a variety of delay intervals. It should be noted that these authorities hold that the amygdala is not part of the MTL memory system, but, with respect to the MTL's remaining structures, the basic proposition is that they work together as a single functional entity. According to the reification theory, damage to each component of the MTL should cause similar behavioral deficits (Zola-Morgan et al., 1994). We acknowledge that some might view this formulation as one that oversimplifies a more nuanced theory (S. Zola, personal communication), but we rely here on a fair reading of the published record, one that leads to testable and falsifiable hypotheses.

Although the reification theory dominates the field, not all experts share a high level of enthusiasm for it. For example, Murray and her colleagues have argued that the MTL consists of multiple functional subdivisions (Murray, 1996; Murray, Bussey, Hampton, & Saksida, 2000). In addition, Gaffan (2002) has argued against the very idea of "memory systems." According to his analysis, the "dense amnesia" that follows damage to the MTL results from interrupting inputs to that region from the basal forebrain, as well as disconnecting the MTL from the prefrontal cortex. He reasoned that the former disconnection, perhaps involving cholinergic inputs, disables plasticity mechanisms in the MTL and that the latter eliminates the contribution of something akin to a global workspace (Baars, Ramsoy, & Laureys, 2003), an information-processing system transcending domain specificity. In other words, according to Gaffan (2002), the MTL is nothing special in the pantheon of telencephalic structures, some parts of it process certain kinds of information, other parts process different information, and damage to each of these parts produces a different set of behavioral deficits (see also Gaffan, 2001; O'Keefe, 1999). In Gaffan's view, the susceptibility to global anterograde amnesia after MTL damage arises from an accident of telencephalic geometry in certain primates. We call this idea—one positing different functions for each of the MTL's many components—the *balkanization theory*.

In view of such doubts, how did the reification theory gain such wide acceptance? This process began with the unfortunate neurosurgical outcome mentioned above for the patient H.M.: the unintentional production of a severe and relatively selective amnesia, mainly anterograde in nature, through surgical ablation of large parts of his MTL. Attempts to mimic H.M.'s amnesia in monkeys met, at first, with little success. In early studies, monkeys with bilateral removals of the amygdala, hippocampus, and underlying cortex—a lesion designed to mimic the MTL damage in H.M.—could learn and remember as well, or nearly as well, as intact monkeys (Correll & Scoville, 1965; Orbach, Milner, & Rasmussen, 1960). Monkeys with such lesions could remember cued places for both short and long periods of time and could learn and remember which of two objects to choose to obtain food. These and other early investigators did not know whether their negative results occurred because of differences between humans and monkeys, differences in the structures damaged, or weaknesses of the methods used to assess learning and memory in monkeys. Although early thinking focused on the first of these possibilities, the third is now widely acknowledged to have played the largest role in these early failures.

By the mid-1970s, both Gaffan and Mishkin began using various matching tasks, such as the DNMS task, to evaluate memory in monkeys with MTL damage. Although matching tasks had been used previously, the versions used by Gaffan and Mishkin employed novel stimuli on each trial (Mishkin & Delacour, 1975), and, in addition, taxed memory by requiring the monkeys to remember lists of items or single items over increasingly longer delay intervals (Gaffan, 1974). Gaffan (1974) transected the fornix in a group of monkeys and reported that they showed a memory deficit as assessed by the delayed matching-to-sample task. This finding appeared to support the initial speculation about the cause of H.M.'s anterograde amnesia, which focused on a potential contribution of the hippocampus. But in 1978, Mishkin reported that combined—but not separate—removals of the amygdala and hippocampus led to severe impairments in visual recognition memory as measured by the DNMS task. The monkeys with the combined lesions could relearn the rule and could perform well when required to remember items over short (~10 s) delay intervals, but scored near chance levels when required to remember items for 60 s or more (Mishkin, 1978). Accordingly, Mishkin concluded that combined damage to the amygdala and hippocampus caused the global anterograde amnesia in H.M. Several additional studies provided evidence that seemed to verify Mishkin's idea (Bachevalier, Parkinson, & Mishkin, 1985; Murray & Mishkin, 1984; Saunders, Murray, & Mishkin, 1984; Zola-Morgan & Squire, 1984, 1985; Zola-Morgan, Squire, & Mishkin, 1982), but his conclusion did not hold up in the long run (see Section 4). Nevertheless, it was highly influential in forging the reification theory of MTL function: The idea that damage to one part of the MTL did little, but damage to two or more parts did much, soon became the prevailing view.

There are two additional pillars of the reification theory. If the MTL is a "thing" that provides the mechanisms for a declarative memory system, then there must be other "things" that provide the mechanisms for other "systems." These other "things" and "systems" involve perception and procedural memory. Regarding perception, Zola-Morgan et al. (1994) reviewed data obtained from tasks which they thought tested either declarative memory or perception in relative isolation from the other. For example, removals of the perirhinal cortex and hippocampus, two major parts of the MTL, were said to disrupt performance on two "memory" tasks but not on a "perception" task. Conversely, damage to sensory areas of cortex, outside the boundaries of the MTL, were said to cause a selective deficit on the same "perception" task (Buffalo, Stefanacci, Squire, & Zola, 1998b). Furthermore, in accord with the reification theory, Zola-Morgan et al. (1994) concluded that lesions of the hippocampus and of the perirhinal cortex yield the same behavioral effect. Regarding procedural memory, the evidence taken as support for the idea that yet another "thing," the basal ganglia, mediates those forms of memory has been recited so often that its principal tenets need not be recapitulated here (see, for example, Packard & Knowlton, 2002).

We turn to evidence that casts doubt on the reification theory of MTL function in Section 4, but first we present some new ideas from theoretical neuroanatomy that put the MTL in a new perspective.

3. Beyond textbook anatomy

What makes up the MTL of primates? This question can be answered at several levels. At one level, the answer could be the hippocampus, amygdala, entorhinal cortex, perirhinal cortex, and parahippocampal cortex. Fig. 1 shows this view of the MTL in schematic form, and Fig. 2 shows the configuration of some of these structures in the primate brain. At a finer level, a number of additional components could be mentioned: the many subdivisions of the hippocampal complex, including the subiculum proper, presubiculum, parasubiculum, prosubiculum, dentate gyrus, and cortical fields CA1–CA4; the many subdivisions of the amygdala; and so forth. The hippocampus and subiculum can both be divided into septal and temporal parts, often termed dorsal and ventral, respectively, in rodents, and typically called posterior and anterior, respectively, in humans. So the MTL contains a lot of "things." This fact, alone, seems at odds with the reification theory of MTL function. But is there some other way to look at all of these "things"?

Recent neuroanatomical work, most closely associated with Swanson and his colleagues, leads to a new view of the MTL and many of its components. Fig. 1 color codes the major components of the MTL in terms of their cytoarchitecture, in part following Swanson's views. Some parts of the MTL have the three-layered structure of allocortex, which evolved very early in vertebrate history (Aboitiz, Montiel, Morales, & Concha, 2002; Neary, 1990; Northcutt, 1996, 2001; Striedter, 1997; Ulinski, Larson-Prior, & Slater, 1991; Wicht & Northcutt, 1992, 1998). Other parts of the MTL have the structure of neocortex, which evolved only recently, with the advent of mammals (see Aboitiz et al., 2002; Striedter, 1997; Ulinski et al., 1991). There is a great deal of confusion associated with these cytoarchitectonic classifications, much of it stemming from the writings of Sanides and his followers. Vaguely defined terms such as juxtallocortex, periallocortex, and proisocortex have been used to support a majestically uninformed theory of brain evolution. Another source of confusion is the fact that the term isocortex is synonymous with neocortex, but this usage is not always explained. Most pertinent to our presentation is that fact that perirhinal

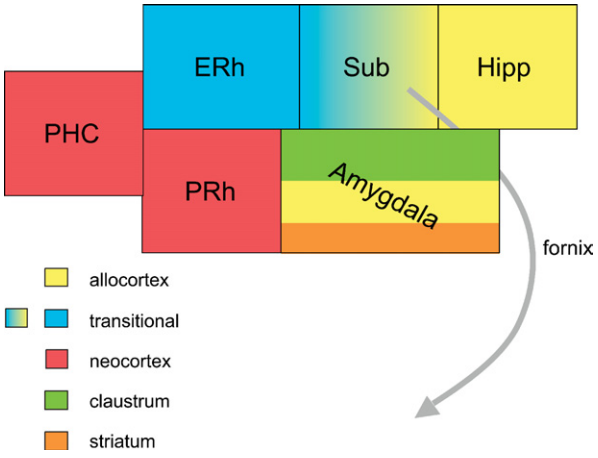


Fig. 1. The major components of the medial temporal lobe (MTL) in primates. The color code corresponds to different cortical and subcortical architectures. *Abbreviations:* ERh, entorhinal cortex; PHC, parahippocampal cortex; PRh, perirhinal cortex; Hipp, hippocampus; Sub, subiculum.

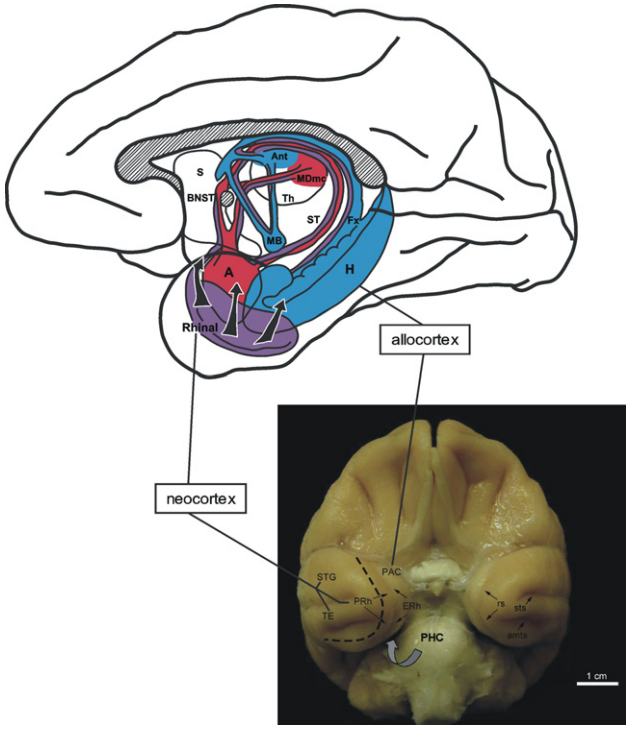


Fig. 2. The locations of major components of the MTL in primates. Upper left: A drawing of the medial view of a macaque brain showing the location of selected components of the MTL and some of the major pathways emanating from them. Lower right: A photograph of a ventral view of a macaque brain, with rostral up, caudal down, and ventral out from the page. The dashed line indicates the boundary between the perirhinal cortex and areas TE (ventrally) and STG (dorsally). Note that other investigators place the boundary somewhat more laterally, in or near the anterior middle temporal sulcus (amts). *Abbreviations:* A, amygdala; amts, anterior middle temporal sulcus; Ant, anterior nuclei of the thalamus; BNST, bed nucleus of the stria terminalis; ERh, entorhinal cortex; Fx, fornix; H, hippocampus; MB, mamillary bodies; MDmc, magnocellular division of the mediodorsal nucleus of the thalamus; PAC, peri-amygdala cortex; PHC, parahippocampal cortex, which cannot be seen in the photograph; PRh, perirhinal cortex; Rhinal cortex, perirhinal plus entorhinal cortex; rs, rhinal sulcus; S, septal nuclei; ST, stria terminalis; STG, superior temporal gyrus, sts, superior temporal sulcus; TE, part of the inferior temporal cortex; Th, thalamus.

cortex is often held to be "not quite" neocortex, based on criteria such as an unimpressive internal granular layer, layer 4, through much of its extent. Similar comments have sometimes been made about the parahippocampal cortex. However, many neocortical areas lack layer 4, including the primary motor cortex, the premotor cortex, and several cingulate areas. Perirhinal cortex in both rats and macaque monkeys and parahippocampal cortex in monkeys have clearly discernable layers 2, 3, 5, and 6 (Suzuki & Amaral, 2003; for monkeys, Swanson, 2004; for rats), which makes their classification as neocortex (equivalently, isocortex) unambiguous. But having neocortex does not make the MTL unusual: all of the major lobes of the cerebrum have a great deal of neocortex. Unlike the frontal, parietal, and occipital lobes, however, the MTL has large allocortical areas such as the hippocampus and smaller allocortical structures such as the amgydalo–hippocampal transition area, the amygdalo–piriform transition area, and the cortical nuclei of the amygdala. (Other lobes have some small allocortical regions such as the taenia tecta and the induseum griseum.) Fig. 1 also color codes some parts of the amygdala as "striatal" and other parts as "cortical" or "claustral." Putting the claustrum aside for the time being, what is the evidence for these designations?

Swanson based his ideas on evidence from traditional neuroanatomical methods (Petrovich, Canteras, & Swanson, 2001; Swanson, 2000; Swanson & Petrovich, 1998), such as studies of cell morphology, neuronal connectivity, neurotransmitter expression, and the sources of different structures during development. No one piece of evidence is, by itself, conclusive (Swanson, 2000), and neuroanatomists—at least those who take these ideas seriously—will be arguing about them for a long time. It will not be difficult to find experts who dismiss Swanson's views out of hand. They will suggest that the features described as common to these various parts of the striatum, for example, are only superficial similarities. Although we have no intention here of presenting a critical analysis of Swanson's ideas—our goal is rather to explore some of their implications for understanding the organization and function of the MTL—we believe these ideas from theoretical neuroanatomy deserve serious consideration.

As illustrated in Fig. 1, Swanson views some nuclei of the amygdala as "striatal." The parts of the amygdala that Swanson interprets as striatal—the central and medial nuclei of the amygdala and the anterior amygdaloid area—have neurons that look like medium spiny

neurons in the traditionally recognized parts of the striatum. In addition, these cells express GABA and co-transmitters typical of medium spiny neurons, project to other GABAergic neurons that, like traditionally recognized pallidal neurons, project both to the thalamus and brainstem. These nontraditional parts of the stria-

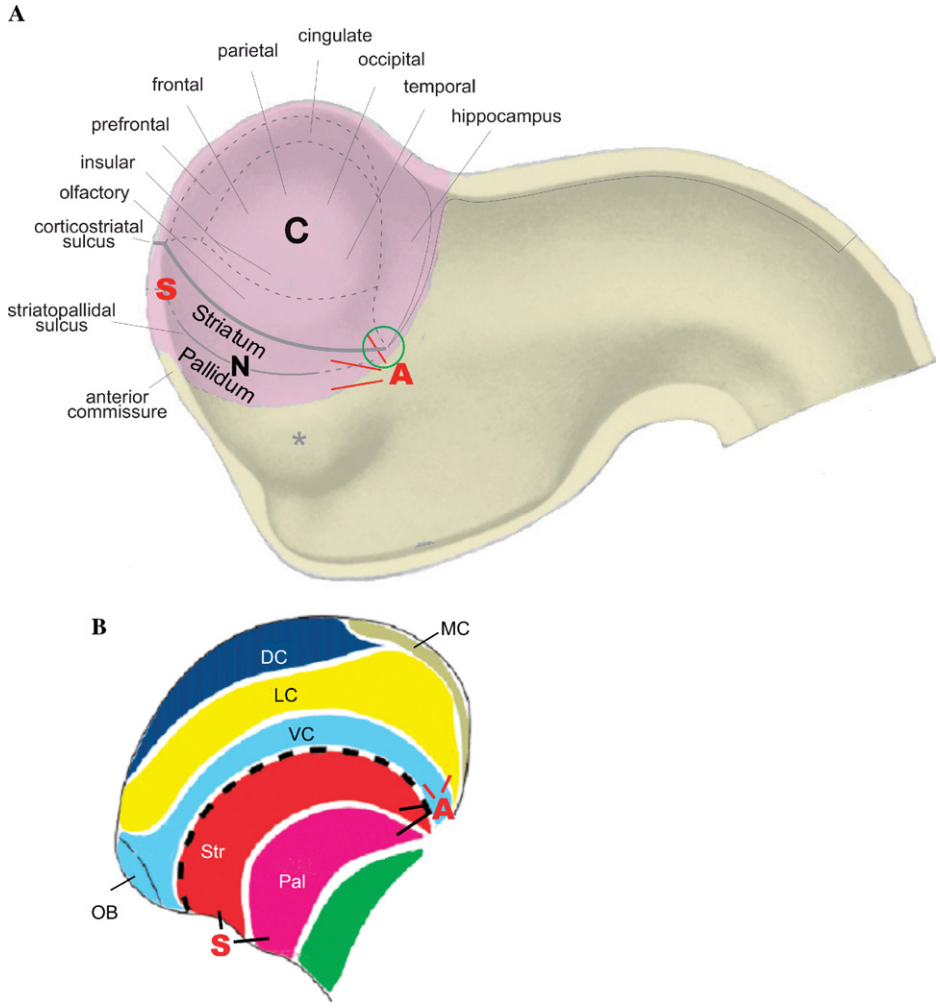
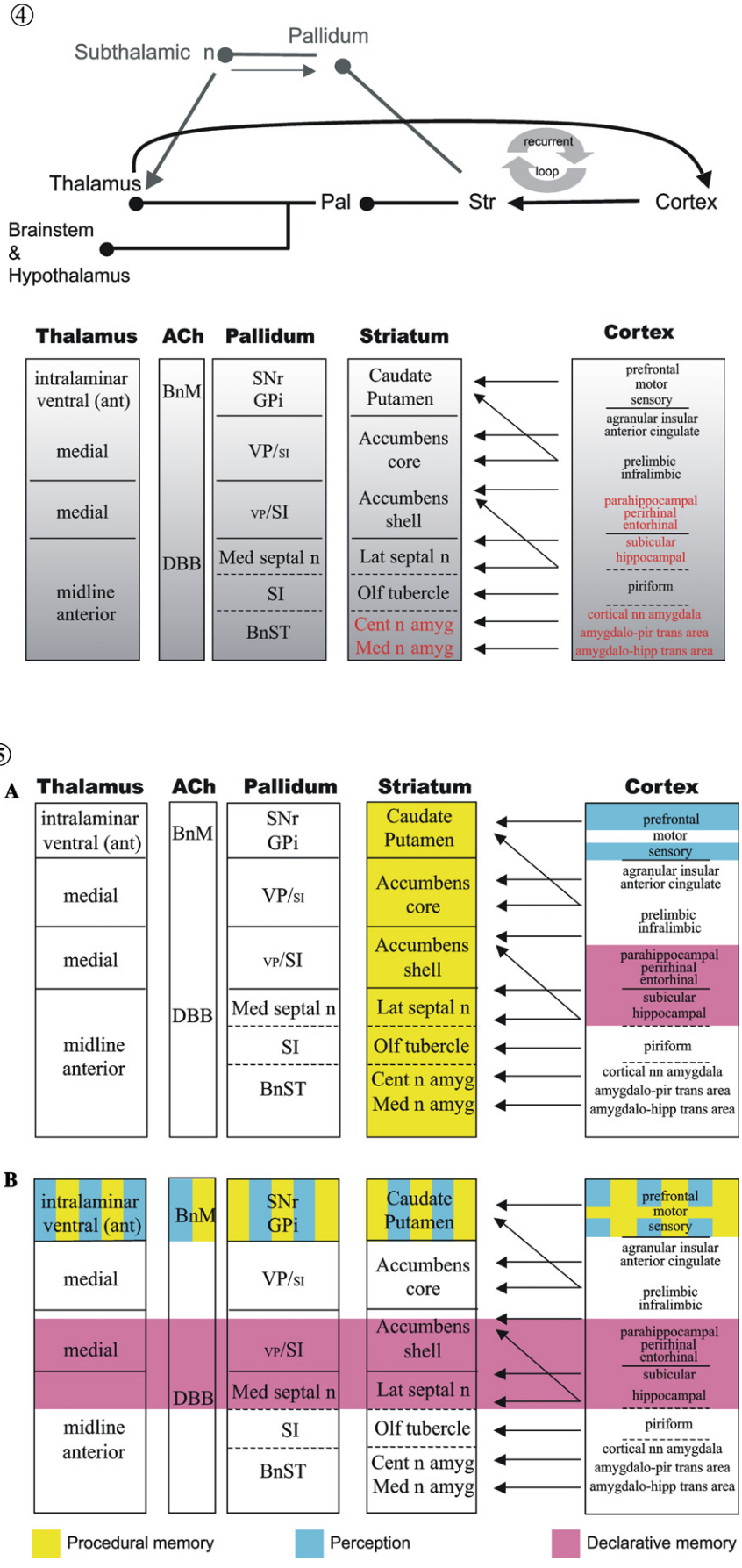


Fig. 3. The convergence of traditional anatomy and embryology with the expression domains of developmental regulatory genes. (A) The forebrain of a 4- to 5-week-old human embryo, from Swanson (2000). The telencephalic vesicle, in pink, gives rise to the entire cortex (C) and basal ganglia (N), including the structures collectively called the amygdala (designated by the red A) and the septal nuclei (designated by the red S). The sources of the various parts of the cerebral cortex are noted, along with other structures of interest. (B) Modified from Puelles et al. (2000). Each color corresponds to a characteristic pattern in the expression of developmental regulatory genes. The amygdala (red A) consists of the caudal aspects of cortex, striatum and pallidum; the septal nuclei (red S) consist of the rostral parts of the striatum and pallidum. Green circle is located at the junction of the basal forebrain with the temporal lobe. *Abbreviations:* A, amygdala; C, cerebral cortex; DC, dorsal cortex; LC, lateral cortex (largest and lateral part of piriform cortex); MC, medial cortex (hippocampus); OB, olfactory bulb; VC, ventral cortex (medial part of piriform cortex, directly adjacent to the lateral olfactory tract); N, basal ganglia; Pal, pallidum; S, septal nuclei; Str, striatum; *, basal forebrain. Reprinted from Swanson (2000), with permission from Elsevier.

Fig. 4. Parallel architecture of cortical–basal ganglionic loops, including those involving allocortex. Structures in red text indicate that they are components of the MTL. *Abbreviations:* ant, anterior; BnM, basal nucleus of Meynert; BnST, bed nucleus of the stria terminalis; Cent n amyg, central nucleus of the amygdala; DBB, diagonal band of Broca; GPi, internal segment of the globus pallidus; hipp, hippocampal; Lat septal n, lateral septal nuclei; Med n amyg, medial nucleus of the amygdala; Med septal n, medial septal nuclei; nn, nuclei; Olf tubercle, olfactory tubercle; Pal, pallidum; pir, piriform; SI, substantia innominata; SNr, reticular part of the substantia nigra; Str, striatum; trans, transition; VP, ventral pallidum. Note that the arrows evoke only a fraction of the relevant connectivity.

Fig. 5. Cortical–basal ganglionic modules in the context of the reification theory. (A) Putative functions of forebrain structures according to canonical reification theory. (B) Putative functions of forebrain structures if reification theory is modified to take into account the theoretical neuroanatomy of the forebrain according to Swanson and his colleagues. Note that the presentation of this figure should not be taken as an endorsement of the view depicted; rather, it provides a framework for reconsideration. Abbreviations as in Fig. 4.


④
Subthalamic n
Pallidum
recurrent
loop
Thalamus
Pal
Str
Cortex
Brainstem
&
Hypothalamus
Thalamus
ACh
Pallidum
Striatum
Cortex
intralaminar
ventral (ant)
medial
medial
midline
anterior
BnM
DBB
SNr
GPi
VP/SI
VP/SI
Med septal n
SI
BnST
Caudate
Putamen
Accumbens
core
Accumbens
shell
Lat septal n
Olf tubercle
Cent n amyg
Med n amyg
prefrontal
motor
sensory
agranular insular
anterior cingulate
prelimbic
infralimbic
parahippocampal
perirhinal
entorhinal
subicular
hippocampal
piriform
cortical nn amygdala
amygdalo-pir trans area
amygdalo-hipp trans area
⑤
A
Thalamus
ACh
Pallidum
Striatum
Cortex
B
Procedural memory
Perception
Declarative memory

tum, like the traditionally recognized parts, receive inputs from dopamine neurons in the brainstem and from both the dorsal thalamus and the cerebral cortex. The same observations hold for the lateral septal nucleus, which Swanson also believes to be part of the striatum. Furthermore, both the striatal parts of the amygdala and the lateral septal nucleus derive from a part of the embryonic telencephalon—the region between the corticostriatal sulcus and the striatopallidal sulcus—that gives rise to the traditionally recognized parts of the striatum (Fig. 3A). The lateral septal nucleus (S) derives from its rostral part and the striatal parts of the amygdala (A) derive from its caudal part. Like the traditionally recognized parts of the striatum, these nontraditional parts participate in recurrent modules, commonly known as "loops," which include cortical, striatal, pallidal, and thalamic structures. We take up these concepts below, but first we introduce some independent support for Swanson's ideas.

Puelles et al. (2000, 2001) have studied the expression of developmental regulatory genes in embryonic mice. Fig. 3B illustrates their conclusions. Each of four cortical regions is indicated in a different color, as is the striatum and pallidum, based on patterns of gene expression. Parts of the amygdala express the same regulatory genes in development as do the traditionally recognized parts of the striatum. Others express the cortical or pallidal patterns. Puelles et al. concluded that the parts of the telencephalon traditionally considered to be the amygdala (A) are the caudal aspects of cortex, striatum, and pallidum. These conclusions closely resemble those of Swanson and his colleagues and provide independent support. This analysis also supports Swanson's view that the lateral septal nucleus (S) is a part of the striatum: its most rostral part. Importantly, the cortical nuclei of the amygdala have gene-expression patterns like those of the lateral and ventral cortex (LC and VC, respectively) and unlike those of the dorsal cortex (DC) or the medial cortex (MC). The lateral and ventral cortex compose the piriform cortex, and, in the view of Puelles et al., the cortical nuclei of the amygdala make up their caudal extension. The medial cortex corresponds to the hippocampus. Note the fundamental similarity between these two analyses (Figs. 3A and B) regarding the amygdala (A) and the septal nuclei (S). On both of these views, the amygdala arises from the caudal (and lateral) aspect of the telencephalon, the septal nuclei from a largely rostral (and medial) aspect.

Although the idea that the lateral septal nucleus is part of the striatum seems jarring to those of us who learned textbook neuroanatomy, Swanson (2000) has pointed out that this idea dates to the work of Ramon y Cajal in 1911. In a sense, the caudate and putamen in primates can be considered to be "striatum of the neocortex," and the lateral septal nucleus can be thought of as "striatum of the hippocampus." Further, as Puelles et al. (2000) noted, the idea that the medial and central nuclei of the amygdala are striatal dates to the early 20th century work of Holmgren.

Thus, the MTL in primates seems to be a complex admixture of different cortical and subcortical architectures, some of which evolved very early in vertebrate history, such as the hippocampus (called the medial cortex in Fig. 3B) and parts of amygdala, and others of which evolved relatively recently, such as the parahippocampal and perirhinal neocortex. In the primate brain, these various structures get pushed, during development, into the MTL. So what makes up the MTL? In large part, it consists of the most medial and caudal parts of the cerebral cortex and striatum, distorted by evolutionary and embryological development into a nearly unrecognizable configuration. Their concentration in a region called the MTL in primates is, on this view, more an accident of history than a coherent anatomical construct.

One implication of Swanson's new view of the telencephalon involves what are commonly known as recurrent, basal ganglia loops (DeLong & Georgopoulos, 1981). These loops involve neurons in several different anatomical structures, which interact to function as distributed neural networks, sometimes called distributed modules (Houk & Wise, 1995). As illustrated in the top part of Fig. 4, the prototypical *cortical–basal ganglionic loop* involves connections from cortex to striatum, from striatum to pallidum (via both the direct and indirect striatal-output pathways), from pallidum to thalamus, and from thalamus to cortex. Previous work has focused almost exclusively on the loops that involve neocortex. Accordingly, many of the functions attributed to "the striatum" depend on the traditional view that the striatum consists of the caudate and putamen, which excludes the lateral septal nucleus and the striatal parts of the amygdala, and sometimes even excludes well accepted parts of the striatum such as the nucleus accumbens and other parts of the ventral striatum.

According to the view presented in Fig. 4, the cerebral cortex includes not only the neocortex, but also the hippocampus, the piriform cortex, the cortical "nuclei" of the amygdala, and transitional allocortical areas near the piriform cortex and hippocampus. The associated parts of the striatum include the lateral septal nucleus, the olfactory tubercle, the medial and central nuclei of the amygdala, and the anterior amygdala area. The bottom part of Fig. 4 also captures the idea that each part of the striatum has an associated part of the pallidum, including the medial septal nucleus, the substantia innominata, and the bed nucleus of the stria terminalis (sometimes considered part of the "extended amygdala"). To each cortical–basal ganglionic loop there is also a source of cholinergic (and other) inputs from the basal forebrain, specifically from the diagonal band (of Broca) and the basal nucleus (of Meynert).

In the next section, we will review several lines of empirical evidence that cast doubt on the reification theory (see Section 2), at least in its canonical form. Before we do that, let us examine some of the implications of the ideas sketched above from theoretical neuroanatomy. The reification theory holds that the MTL, as a whole, is a declarative memory system, that the lateral temporal lobe, along with other parts of the neocortex, subserves perception, and that an entity sometimes termed the "basal ganglia," sometimes termed the "striatum," and sometimes termed the "corticostriatal system" provides the mechanism for procedural memory (or equivalently, with varying degrees of rigor, habits). However, by the term striatum, the proponents of the reification theory mean to refer to the caudate and putamen, only, not to the other parts of the striatum mentioned above.

This traditional view of the basal ganglia has not always been explicitly stated, and has often instead been taken for granted. Packard and Knowlton (2002) are among only a few proponents of the reification theory to acknowledge explicitly that functional attributes usually ascribed to the "basal ganglia" or "striatum" are intended to apply only to the most dorsal part of it. However, by limiting their extended concept of the striatum to a less inclusive view than that sketched here, they still seek to find a functional dissociation between entities called the hippocampus and the basal ganglia. Fig. 5 illustrates a problem with that line of thought. It shows that the hippocampus and other allocortical parts of the MTL have their associated parts of the striatum and pallidum, much as the neocortical areas have theirs.

Fig. 5A shows how the reification theory maps onto the main structures of the forebrain according to canonical reification theory. Fig. 5B shows how the same ideas can be modified to bring them more into line with the new ideas about forebrain organization outlined in this section. We emphasize that this exercise should not be construed as an endorsement of the scheme presented in Fig. 5B. We note only that this way of structuring the reification theory avoids the problem of assuming that an entity called the "basal ganglia" or the "striatum" subserves any particular kind of memory, knowledge, or system. Instead, Fig. 5B recognizes that different parts of the basal ganglia have different functions, depending on the cortical–basal ganglionic loops to which they contribute. The difference between Figs. 5A and B reflects a change from traditional "column-wise thinking" in the former to "row-wise thinking" in the latter. It is just another way of looking at the reification theory. But the question remains: Does the reification theory hold up to empirical testing? The next section answers that question.

4. Falsifying the reification theory

4.1. Recognition memory

Despite its popularity, evidence against the reification theory has accumulated rapidly. The history of these studies is elaborated elsewhere (Buckley & Gaffan, 2000; Murray, 1996) and will not be repeated here. Table 1 shows the results of certain experiments assessing stimulus memory. According to the reification theory, the greater the damage to the MTL, the greater should be the impairment in recognition memory as measured by DNMS (Zola-Morgan et al., 1994). Contrary to the prediction of the reification theory, however, combined lesions of the amygdala and hippocampus made with the fiber-sparing excitotoxin ibotenic acid fail to produce impairments on DNMS (Murray & Mishkin, 1998). Furthermore, damage to the entorhinal and perirhinal cortex (also known collectively as the "rhinal cortex") produces a severe impairment (Baxter & Murray, 2001a; Eacott, Gaffan, & Murray, 1994; Meunier et al., 1993; Table 1, Fig. 6). Aspiration lesions of the amygdala do cause mild deficits, but this finding is misleading because it

Table 1
Effects of lesions on stimulus memory

Tasks	H	A(IBO)	A(ASP)	PRh PRh + ERh
Trial-unique DNMS	±(IBO)*	–	+	+ + +
Visual-visual paired association learning	–(ASP)		–	+ + +
Crossmodal DNMS	–(ASP)	–	+ + +	+ + +

The data come from several sources (Buckley & Gaffan, 1998b; Buckley, Gaffan, & Murray, 1997; Buffalo et al., 1999; Goulet & Murray, 2001; Meunier, Bachevalier, Mishkin, & Murray, 1993; Mishkin, 1978; Murray, Gaffan, & Mishkin, 1993; Murray & Mishkin, 1985, 1998; Nemanic, Alvarado, & Bachevalier, 2004). Tests of stimulus memory are listed in the left column. DNMS tests recognition memory of items for up to 40 min, whereas the two other tasks, visual–visual paired-associate learning and crossmodal DNMS, assess long-term associative memory. The right column shows the effects of either selective removals of the perirhinal cortex or combined removals of the perirhinal and entorhinal areas. *Abbreviations:* A(ASP), aspiration lesions of the amygdala, which include nearby areas of cortex and fiber tracts; A(IBO), selective ibotenic acid lesions of the amygdala; ASP, aspiration lesions of the hippocampus; DNMS, the delayed nonmatching-to-sample task; ERh, entorhinal cortex lesions; H, hippocampal lesions; IBO, ibotenic acid lesions of the hippocampus; PRh, perirhinal cortex lesions; +, mild deficit; +++, severe deficit; –, no deficit; ±, deficits in some conditions, but not in others, *some findings (Beason-Held, Rosene, Killiany, & Moss, 1999; Zola et al., 2000) disagree with the conclusion that selective hippocampal lesions and combined lesions of the hippocampus and the amygdala (Fig. 6) have no effect on trial-unique DNMS.

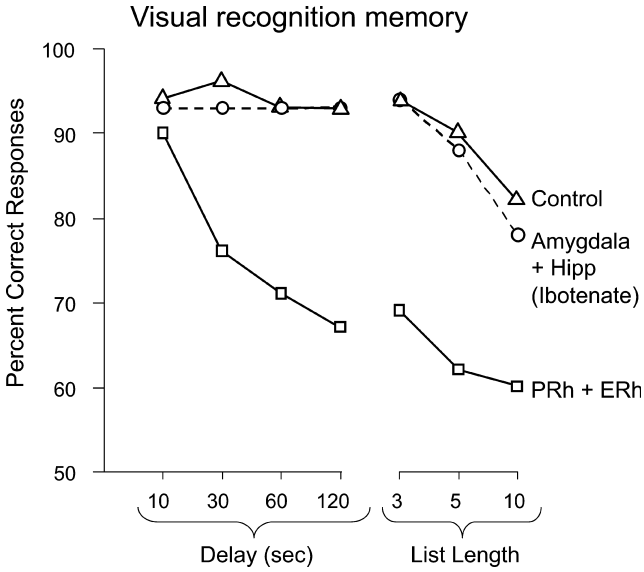


Fig. 6. Lesions of the perirhinal and entorhinal cortex are sufficient to cause a deficit in visual recognition memory, as assessed by the delayed nonmatching-to-sample task (DNMS). Curves on the left show the effects of imposing increasingly longer delays between sample presentation and choice test. Curves on the right show the effects of increasing list length, requiring the memory of multiple objects. After combined, selective excitotoxic lesions of the amygdala and hippocampus (dashed line, circles), performance remains the same as for an unoperated control group (solid line, triangles). In other tests, these animals can perform as well as controls even with delays of about 40 min (Murray & Mishkin, 1998). Monkeys with entorhinal plus perirhinal cortex lesions were severely impaired in object recognition memory (solid line, squares). Data from Meunier et al. (1993) and Murray and Mishkin (1998). *Abbreviations:* Amygdala + Hipp (Ibotenate), monkeys with selective excitotoxic lesions of both the amygdala and the hippocampus, bilaterally ($N = 7$); PRh + ERh, monkeys with combined bilateral aspiration lesions of the perirhinal cortex (PRh) and entorhinal cortex (ERh) ($N = 7$); Controls, unoperated control monkeys ($N = 8$).

fails to take into account additional damage to the cortex of the MTL and fiber pathways passing near the amygdala (Goulet, Doré, & Murray, 2001). Since the original report of Murray and Mishkin (1998), four additional studies have assessed the effect on DNMS of selective hippocampal lesions, two reporting impairment (Beason-Held et al., 1999; Zola et al., 2000) and two reporting no impairment (Buckmaster, Eichenbaum, Amaral, & Rapp, 1999; Nemanic et al., 2004). Although there remains some controversy regarding whether the hippocampus makes *any* contribution to recognition memory as measured by DNMS (as noted by the asterisk in Table 1), there is widespread agreement that the entorhinal and perirhinal cortex are the main substrates of visual recognition as measured by DNMS. In sum, damage to just two parts of the MTL, the perirhinal cortex and the entorhinal cortex, is sufficient to produce nearly the same degree of deficit as would removal of the entire MTL.

There are additional findings involving recognition memory that argue against the reification theory. First, the small effect of hippocampal lesions on tasks such as DNMS may be accounted for by other factors. For example, Baxter and Murray (2001b) conducted a meta-analysis of the studies examining the effects of selective hippocampal damage on the DNMS task in monkeys. They found an inverse relationship between the extent of hippocampal damage and the magnitude of memory loss. That is, paradoxically, the smaller the hippocampal lesion, the greater the impairment in recognition memory as measured by the DNMS task. This finding is the opposite of that predicted by the reification theory, and it could account for the reports of an impairment on the DNMS task after selective hippocampal damage: On this view, small deficits are an artifact of an incomplete lesion, and even more incomplete lesions would lead to yet greater deficits. Although Zola and Squire (2001) have argued that several factors other than this "inverse relationship" are the likely cause of Murray and Mishkin's (1998) failure to detect an impairment on DNMS in monkeys with selective hippocampal lesions, most of these possibilities (e.g., one vs. two stages of surgery; preoperative vs. postoperative training) have been ruled out by the findings of Nemanic et al. (2004) and the preliminary findings of Buckmaster et al. (1999). Specifically, Buckmaster et al. showed that monkeys trained using the same methods as those used by Zola and Squire and their colleagues (including postoperative acquisition of the DNMS task and one-stage surgery) were unimpaired on the DNMS task. Although the extent of the lesions in these monkeys has not yet been assessed quantitatively, the results add weight to the negative evidence reported by Murray and Mishkin (1998). And the recent report by Nemanic et al. (2004), who likewise found no impairment on DNMS after selective hippocampal lesions in monkeys that sustained one-stage surgery, provides additional support. Evidently, monkeys with selective, excitotoxic hippocampal lesions can be unimpaired on DNMS. Yet another problem for the reification theory is the report by Meunier, Hadfield, Bachevalier, and Murray (1996), who found that hippocampal lesions, when added to rhinal cortex lesions, yielded a slightly (and significantly) smaller impairment in recognition memory than rhinal cortex lesions alone. This unexpected finding suggests that structures in the MTL interact in memory in a complex way, voiding the simple predictions of the reification theory. Finally, it appears that removals of the parahippocampal cortex, another component of the putative MTL memory system, fail to yield deficits on DNMS (Nemanic et al., 2004).

If damage to the perirhinal and entorhinal cortex can account for almost the entire recognition memory impairment that follows MTL lesions (Hadfield, Baxter, & Murray, 2003), and if neither the hippocampus nor parahippocampal cortex is necessary for DNMS, what does this imply for the reification theory? One position

would be to reject DNMS as a measure of declarative memory, thereby preserving reification theory. But if this stance were adopted, then the only remaining measures of declarative memory in monkeys would be single-pair object discrimination learning (Zola-Morgan et al., 1994), and perhaps tests of preferential viewing. Thus, although Zola-Morgan and Squire (1985) started with the idea that a battery of four tasks (including delayed retention of single object discriminations, concurrent object discrimination learning, delayed response, and DNMS) "tapped" declarative memory, it is now clear that it is difficult to be certain which, if any, of these tasks are specific measures of declarative memory in monkeys. For example, concurrent object-discrimination learning was found to be more sensitive to damage to area TE (part of the inferior temporal cortex) than to damage to the MTL, and this task was therefore discarded as a test of declarative memory (Buffalo, Reber, & Squire, 1998a). In addition, the evidence for involvement of MTL structures in single-pair discrimination learning, a topic taken up in detail below, is equivocal, as is the status of this task as an unambiguous measure of declarative memory. And the preferential viewing task suffers from similar problems. Indeed, we argue that all supposed tests of "declarative" memory should be treated with skepticism. Also, consider the following scenario: What if the relevant findings had been reported in reverse order, with the dramatic effects of rhinal cortex damage on performance of the DNMS task being reported first? In this counterfactual, it is doubtful whether the present controversy concerning the hippocampal contributions to recognition memory—which mainly amounts to an argument over whether that contribution is small or none—would even exist.

In sum, it appears that the perirhinal cortex, in conjunction with the entorhinal cortex, plays a central role in recognizing objects. The weight of evidence suggests that the other parts of the entity called the MTL have little or no role in this function. The next section also presents evidence contrary to the reification theory. The perirhinal cortex appears to play an important role in both the perception and memory of objects and in establishing associations among objects, including abstractions such as progress toward a goal (Liu, Murray, and Richmond, 2000).

4.2. Perception vs. memory

Another tenet of the reification theory is that the MTL is not involved in the perceptual processing of complex visual stimuli. This idea is based, in part, on the findings that lesions of two major parts of the MTL (the hippocampus and the perirhinal cortex), disrupt performance on two "memory" tasks, visual DNMS and single-pair visual discriminations, but not on a "perception" task, concurrent visual discrimination. By contrast, lesions of lateral temporal cortical area TE, in addition to yielding impairment on the DNMS task, yield the opposite pattern of results for the two types of discrimination learning, that is, impairment on the acquisition of concurrent discriminations (the so-called "perception" task), but not on learning single-pair sensory discrimination, the task regarded as memory specific (Buffalo et al., 1999). These and other findings led these investigators (Buffalo et al., 1998a, p. 388) to the conclusion that "the perirhinal cortex is not involved in the perceptual processing of complex visual stimuli." In short, the extra-MTL sensory cortex subserves a "perception system," whereas the MTL subserves a declarative memory system. But what if the cognitive labels that these authors give to their tasks fail to correspond with the underlying cognitive processes? Such labels can be misleading and always demand a high level of skepticism and scrutiny, an admonition that applies to all of the cognitive labels used in this paper, as well.

There is now strong evidence that at least one part of the MTL, the perirhinal cortex, plays a role in perception as well as memory, in distinct conflict with the reification theory. When sensory discrimination requires the disambiguation of complex, conflicting stimulus features, perirhinal cortex becomes essential to performance. On this view, the perirhinal cortex participates both in visual memory, as one subdivision of the MTL, and in visual perception, as part of the ventral stream object analyzer pathway (Buckley & Gaffan, 1998a, 1998b, 1998c, 2000; Bussey & Saksida, 2002; Bussey, Saksida, & Murray, 2002; Eacott et al., 1994; Murray & Bussey, 1999).

Here we discuss two sets of experiments that have been carried out to test this idea. In one, the results of which are illustrated in Fig. 7, control monkeys and monkeys with aspiration lesions of perirhinal cortex were assessed for their rate of acquisition of a series of concurrent visual discriminations. In these experiments, the number of object pairs was held constant, but the degree of feature ambiguity was varied systematically. Feature ambiguity is a property of visual discriminations that emerges when features appear as part of both rewarded and unrewarded objects. Monkeys were tested in three conditions. In the first of these, called Maximum Feature Ambiguity, all features were explicitly ambiguous (AB+, CD+, BC−, AD−, also known as the biconditional problem). In the biconditional problem, the correct choice depends on the combination of features. For example, it is correct to choose A in the presence of B, but not in the presence of D. All features are "balanced" in this way, so that correct choices cannot be guided by any single feature, but only by the combination of features. In another condition, called Minimum Feature Ambiguity, no features were explicitly ambiguous (AB+, CD+, EF−, GH−). In a third condition, called Medium Feature Ambiguity, half the features

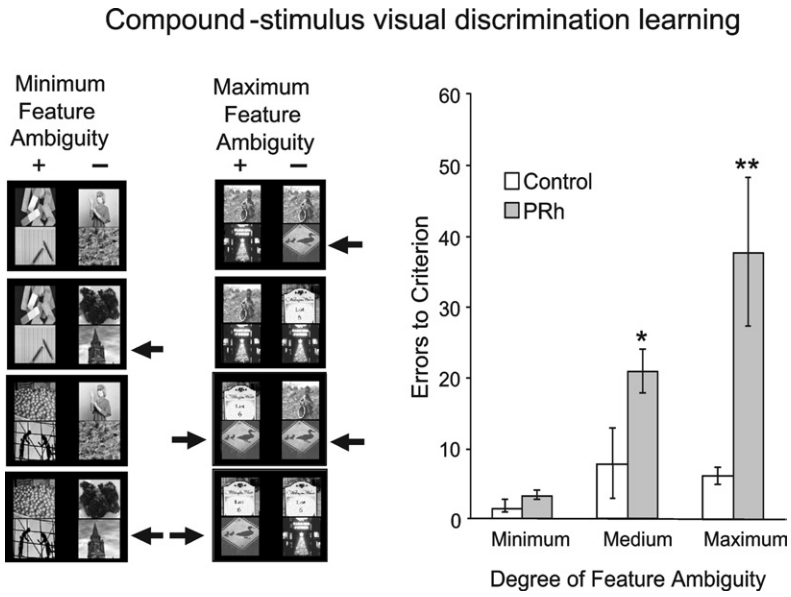


Fig. 7. Lesions of the perirhinal cortex cause deficits dependent on feature ambiguity: discriminating compound stimuli. The left side of the figure shows some of the stimuli used in this experiment. In the Minimum Feature Ambiguity condition, each component of a given, two-part stimulus was either always rewarded when chosen (+) or never rewarded (−). That is, every part of each compound stimulus that was not rewarded (arrows) was never rewarded and every part that was rewarded was always rewarded. In the Maximum Feature Ambiguity condition, every part of each compound stimulus was both rewarded (for one part, arrows to the left of the pictures) and not rewarded (arrows to the right of the pictures) equally. The right side of the figure shows errors to criterion. Data are averaged over several problems of each type. With minimum feature ambiguity, monkeys with perirhinal cortex lesions are unimpaired relative to controls, but as feature ambiguity increased, the monkeys with perirhinal cortex lesions were increasingly and significantly (*, **) impaired. Data from Bussey et al. (2002). *Abbreviations:* PRh, monkeys with bilateral aspiration lesions of perirhinal cortex ($N = 4$); Control, unoperated control monkeys ($N = 4$); Minimum, Medium, and Maximum, different levels of feature ambiguity.

were explicitly ambiguous (AB+, CD+, CE−, AF−). It was found that perirhinal cortex lesions yield an increasingly greater impairment on discrimination learning as the degree of feature ambiguity is increased. This result cannot be accounted for by task difficulty because the same monkeys are unimpaired relative to controls on very difficult color discriminations, and other controls for difficulty were carried out as well. In addition, the Maximum Feature Ambiguity condition is not any more difficult than the Intermediate condition for the control group of monkeys.

These results suggest that a function of perirhinal cortex is to resolve feature ambiguity in complex visual discriminations. The proposal is that the perirhinal cortex performs this function by representing conjunctions of features. Lesions in this region compromise the representation of visual stimuli, and because both accurate perception and accurate memory require accurate representation, both memory and perception are affected by damage to the perirhinal cortex.

If this interpretation is valid, then perirhinal cortex lesions should also cause an impairment on simple, single-pair visual discriminations that exhibit feature ambiguity. To test this idea, in a second experiment Bussey, Saksida, and Murray (2003) manipulated feature ambiguity by morphing (or blending) two pictures. Monkeys were required to learn visual discriminations under conditions of high or low feature ambiguity. The low feature ambiguity condition used two randomly selected pictures, which were not morphed together. The high feature ambiguity condition used morphed pictures consisting of a stimulus that was roughly 65% of the rewarded stimulus and 35% of the foil vs. one that was 35% of the rewarded stimulus and 65% of the foil. Monkeys were tested for their acquisition of several problems of each type. Fig. 8 shows the result. With low feature ambiguity, the monkeys with perirhinal cortex lesions learned single-pair discrimination problems just as fast as the controls. In the high feature ambiguity condition, the monkeys with perirhinal cortex lesions were impaired relative to controls.

Thus, the two experiments by Bussey et al. (2002, 2003), taken together, support the idea that perirhinal cortex operates as part of the ventral visual stream, or object-analyzer pathway, and that it helps process, represent and store conjunctions of object features. Fig. 9 depicts a model that accounts for the results related here. Of course, the perirhinal cortex does not operate in a vacuum. It interacts with other structures in the brain, and depending on the requirements of the task, it may interact with the hippocampus, the amygdala or the prefrontal cortex in storing information. Gaffan and his colleagues (Buckley & Gaffan, 1998a,

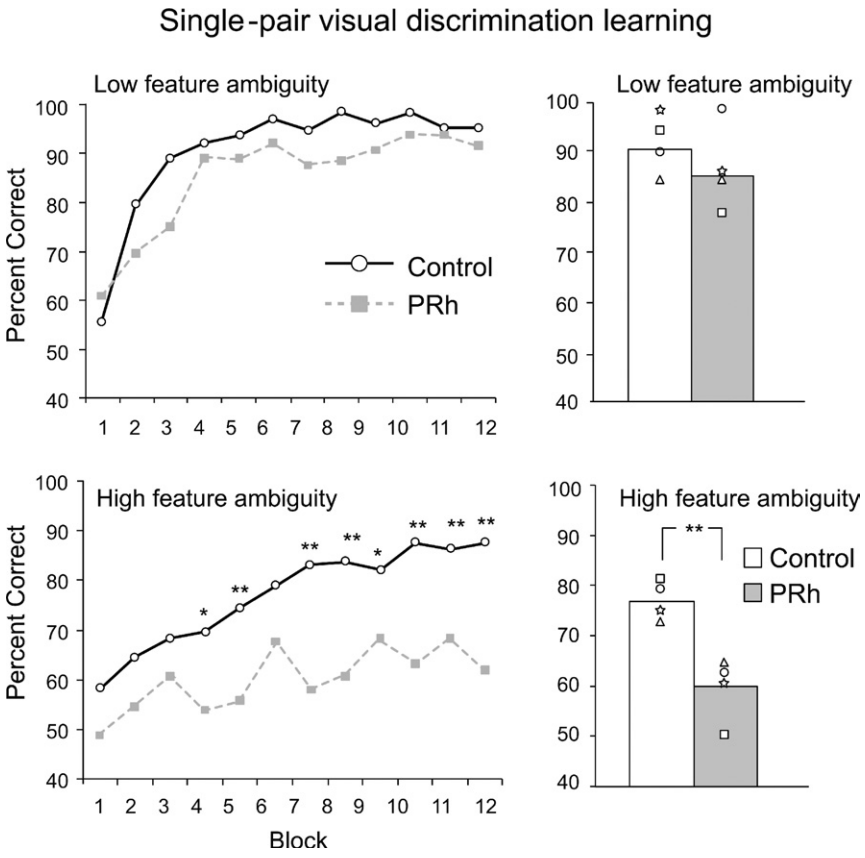


Fig. 8. Lesions of the perirhinal cortex cause deficits dependent on feature ambiguity: discriminating a single pair of morphed stimuli. Left: Percent correct choices as a function of blocks of 8 trials each for low feature ambiguity (top) and high feature ambiguity (bottom) conditions. Significant differences between the groups are marked with asterisks (*, **). Right: The bars show the group data averaged over the total of 96 trials, and symbols indicate the scores of individual monkeys. Results are averaged over several problems of the same type. In acquiring low feature ambiguity discrimination problems, monkeys with perirhinal cortex lesions are unimpaired relative to controls, but in acquiring high feature ambiguity discrimination problems, the monkeys with perirhinal cortex lesions were significantly (**) impaired. Data from Bussey et al. (2003). *Abbreviations:* PRh, monkeys with bilateral aspiration lesions of the perirhinal cortex; Control, unoperated control monkeys.

1998b, 1998c, 2000; Eacott et al., 1994) have used a very different set of tasks and a very different experimental approach to reach much the same conclusion: Perirhinal cortex plays an important role perceptual processing, contrary to the reification theory.

There is another important aspect of the results from the study of single-pair discrimination learning described above. As we have seen, the reification theory depends on the assignment of discrimination learning, in the single-pair format, to declarative memory, in contrast to the concurrent version of visual discrimination learning, which is held to depend on perceptual processes. Indeed, rapid learning is thought to be a defining characteristic of declarative memory (Bachevalier & Mishkin, 1984; Buffalo et al., 1999; Squire, Knowlton, & Musen, 1993; Squire & Zola-Morgan, 1983; Teng, Stefanacci, Squire, & Zola, 2000; Zola et al., 2000). As Zola and Squire (2000, p. 492) expressed this view in a seminal paper on the subject:

> simple two-choice discrimination tasks—that is, ones that are learned quickly by normal animals—are dependent on the [medial] temporal lobe. More difficult two-choice discrimination tasks. . .are independent of the medial temporal lobe.

As illustrated in Fig. 8, the results of Bussey et al. (2003) were inconsistent with the prediction of an impairment on rapidly learned visual discrimination problems, but not slowly learned ones. Indeed, this study yielded the opposite pattern of results. These findings accorded with the countervailing prediction that impairments would occur only on perceptually difficult, slowly learned visual discriminations, those with high levels of feature ambiguity (Bussey & Saksida, 2002; Murray & Bussey, 1999). Thus, in contrast to the idea of Zola and Squire articulated above, the empirical evidence shows that the impairments in single-pair visual discrimination caused by lesions of the perirhinal cortex are related more to perceptual factors than to the speed of learning.

So how can we account for the impairment on single-pair discriminations after perirhinal cortex damage reported by Buffalo and her colleagues (Buffalo et al., 1999; Buffalo, Ramus, Squire, & Zola, 2000) and as

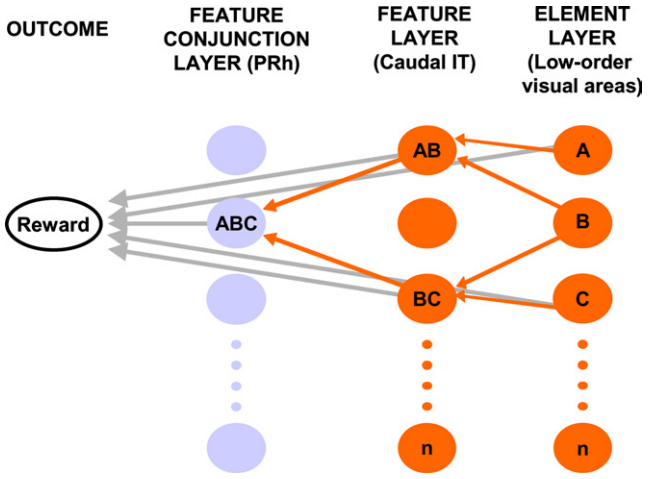


Fig. 9. Model accounting for feature ambiguity effects. According to this model, networks of neurons (ellipses) in caudal regions of the ventral visual stream represent elemental features (Element layer) or simple conjunctions of features (Feature layer). Each element is denoted by a capital letter (A, B, and C). More rostral regions, such as perirhinal cortex, represent more complex conjunctions of these features (ABC). *Abbreviations:* IT, inferotemporal cortex; PRh, perirhinal cortex. Adapted from Bussey and Saksida (2002).

confirmed by Hampton and Murray (2002)? One possibility is that the objects being discriminated had enough feature overlap to yield an impairment on the discrimination task. Although the idea of feature ambiguity was not assessed, Buffalo et al. (1999) used four different pairs of objects, administered serially, to assess single-pair discrimination learning. At least 3 of the 4 object discriminations appear to involve relatively high levels of feature ambiguity. For example, one pair consisted of red and green peanut shells, another of white and black rectangles, and yet another of yellow and pink plastic eggshells. In each case, although the items differed in color, they had the same shape and size, thereby exhibiting feature overlap for these dimensions. Thus, feature ambiguity might account for the impairment on single-pair discrimination of monkeys with perirhinal cortex lesions.

More recently, in an attempt to extend our analysis of perirhinal cortical contributions to perception, we have employed the transverse patterning task. In this study, to assess the contributions to learning by various MTL structures, we compared directly the effects of selective hippocampal lesions with those of perirhinal cortex lesions (Saksida, Bussey, Buckmaster, & Murray, 2003). This task is created by taking three objects, A, B, and C, and pairing them in such a way that when A is paired with B, A is rewarded; when B occurs with C, B is rewarded; and when C occurs with A, C is rewarded. In the notation used above, the task involves three problems: A+ vs. B−, B+ vs. C−, and A− vs. C+. These three problems are mixed together within sessions, and the measure of interest, as before, is the rate of acquisition. Note that the transverse patterning problem has exactly the same characteristics as the foregoing discrimination problems that we arranged for the high feature ambiguity condition, only now at an object level. That is, across the three individual discrimination problems, every object is both rewarded and unrewarded.

The "objects" in this task, as in our earlier experiment, were complex grayscale pictures. On each trial, monkeys were presented with a single pair of objects, one object on the left and one on the right side of the screen, and they were required to touch one stimulus on the screen to indicate their choice. The monkeys learned through trial and error which stimulus, when touched, resulted in delivery of a food reward. Because the monkeys with hippocampal lesions were tested later than those with perirhinal cortex lesions, they were accompanied by their own group of unoperated controls. As predicted, monkeys with perirhinal cortex lesions were impaired relative to the controls. By contrast, monkeys with selective hippocampal lesions were actually facilitated on this task, relative to their controls (Saksida et al., 2003). These data support the idea that the perirhinal cortex, but not the hippocampus, is essential for representing conjunctions of features. In addition, these findings provide the strongest evidence to date against the reification theory; the opposing effects of lesions of the hippocampus, on the one hand, and of perirhinal cortex, on the other, are inconsistent with the idea that these structures are working together as a single functional entity.

Not only does the pattern of data contradict the idea that these structures are working together to support memory, they suggest there is a competition between hippocampal and perirhinal processing in storing information. The facilitation is reminiscent of findings reported by McDonald and White (1995), who found that fornix transection in rats facilitates acquisition of conditioned cue preference. Whereas we found that hippocampal damage facilitates acquisition of a perirhinal-dependent task, transverse patterning, they found that hippocampal damage facilitated acquisition of an amygdala-dependent task, conditioned cue preference.

The work cited here adds to the "overwhelming evidence," in the words of Buckley and Gaffan, that the perirhinal cortex is important for both memory and perception (e.g., Buckley & Gaffan, 1998a, 1998b, 1998c, 2000; Bussey & Saksida, 2002; Bussey et al., 2002, 2003; Eacott et al., 1994; Murray & Bussey, 1999). Thus, we can reject that aspect of the reification theory which holds that the MTL is a thing that subserves declarative memory, but not visual analysis or perception (Buffalo et al., 1998a, 1999; Sakai & Miyashita, 1993; Squire, 1992). It is important to emphasize that these data do not argue against an important role for the perirhinal cortex in memory, only that it does not function exclusively in a mnemonic role. It seems likely that the peri-

rhinal cortex is important for object memory, if for no other reason than its pivotal anatomical position. The perirhinal cortex is reciprocally related to several high-order, modality-specific sensory cortical processing regions and can interact with the hippocampus (indirectly via the entorhinal cortex) and other brain regions such as the prefrontal cortex and dorsal thalamus (Aggleton & Brown, 1999; Bussey, Duck, Muir, & Aggleton, 2000; Bussey, Muir, & Aggleton, 2001; Gaffan & Parker, 1996; Murray, 2000). Rather than considering the perirhinal cortex exclusively as part of a thing called the MTL, it can be considered to be a rostral component of the ventral visual stream, as well. It is not surprising, in this context, that the perirhinal cortex functions in both perception and memory: it processes and stores representations of complex visual stimuli (Bussey & Saksida, 2002; Bussey et al., 2002; Murray & Bussey, 1999).

Finally, it is worth noting that complete, selective, excitotoxic amygdala lesions do not disrupt the learning of rapidly acquired discrimination problems (Malkova, Gaffan, & Murray, 1997). There are other examples of intact instrumental learning in rats with amygdala damage (Blundell, Hall, & Killcross, 2001; Burns, Robbins, & Everitt, 1993). Of course, these findings do not imply that, in the absence of an amygdala, animals learn discrimination problems in an entirely normal manner, but it does indicate that there is a mechanism outside the amygdala that can mediate this type of learning. Thus, single-pair sensory discrimination learning is not a function of the MTL per se, but rather depends on the contribution of a particular subset of its components.

4.3. Stimulus–response associations and spatial tasks

As we have seen, the reification theory fails to account for the feature-ambiguity results. What about other tasks? Table 2 shows some of the effects of hippocampal lesions on tests of spatial memory. It has long been thought, based on studies using aspiration lesions, that hippocampal damage produced a severe impairment on tasks such as spatial reversal learning (Jones & Mishkin, 1972; Mahut, 1971), spatial DNMS (Mahut & Moss, 1986), and object–place association (Parkinson et al., 1988). Indeed, these are some of the classic neuropsychological findings cited in support of a role for the hippocampus in spatial memory in monkeys. More recently, however, studies using selective excitotoxic lesions have failed to find the same impairments. Remarkably, selective excitotoxic lesions of the hippocampus in monkeys have been reported to yield no impairment on spatial reversal learning (Murray et al., 1998), no impairment on spatial DNMS (Murray & Mishkin, 1998), and no impairment on object–place association (Malkova & Mishkin, 2003). For one task, object–place association, impairments appear to follow damage to the parahippocampal cortex, the cortical region directly underlying the hippocampus, rather than the hippocampus (Malkova & Mishkin, 2003). This finding presents yet another argument against the reification hypothesis. As with the results on recognition memory using the DNMS task, and as with the results on visual discrimination using the feature-ambiguity tasks, these spatial tasks depend on particular components of the MTL. Damage to those components produces impairments comparable to much larger lesions that include the key area, rather than producing larger deficits as predicted by the reification theory. Table 3 shows similar data for other tasks. The rule seems to be that different parts of the MTL perform different functions, not that they all contribute to the same functions.

In addition to the results summarized in Tables 2 and 3, there is additional evidence for a division of labor among the various parts of the MTL. According to

Table 2
Excitotoxic vs. aspiration lesions of the hippocampus

	H(IBO)	H(ASP)	PHC
Spatial reversals	–	++	
Spatial DNMS	–*	+++	
Object–place association	–	+++	+++

The data come from several sources (Jones & Mishkin, 1972; Mahut, 1971; Mahut & Moss, 1986; Malkova & Mishkin, 2003; Murray & Mishkin, 1998; Murray, Baxter, & Gaffan, 1998; Parkinson, Murray, & Mishkin, 1988). *Abbreviations:* DNMS, the delayed nonmatching-to-sample task; H(IBO), selective, ibotenic acid lesions of the hippocampus; H(ASP), aspiration lesions of the hippocampus, which include the parahippocampal cortex; PHC, parahippocampal cortex lesions; ++, moderate deficit; +++, severe deficit; –, no deficit.

* Although testing in a manual test apparatus yields no impairment, open-field testing does yield impairment on a delayed spatial matching-to-sample task (Hampton, Hampstead, & Murray, 2004).

Table 3
Excitotoxic vs. aspiration lesions of the amygdala

Task	A(IBO)	A(ASP)	PRh PRh + ERh
Object reversals	–	+ + +	+ + +
Visual discrimination Aud. 2° reinforcement	–	+ + +	+
Visual discrimination learning set		+	+
Win-stay, lose-shift	±	+	

Data are from several sources (Baxter, Hadfield, & Murray, 1999; Baxter & Murray, 2001a; Gaffan & Harrison, 1987; Gaffan & Murray, 1990; Izquierdo, Suda, & Murray, 2003; Jones & Mishkin, 1972; Malkova et al., 1997; Murray et al., 1998; Spiegler & Mishkin, 1981; Stefanacci, Clark, & Zola, 2003). The right column shows the effects of either selective removals of the perirhinal cortex or combined removals of the perirhinal and entorhinal areas. *Abbreviations:* A(ASP), aspiration lesions of the amygdala, which include nearby areas of cortex and fiber tracts; A(IBO), selective ibotenic acid lesions of the amygdala; Aud. 2° reinforcement, auditory secondary reinforcement. ERh, entorhinal cortex lesions; PRh, perirhinal cortex lesions; +, mild deficit; +++, severe deficit; –, no deficit; ±, mild, transient deficit.

reification theory, stimulus–response associations are not the province of the MTL, but of the basal ganglia. And, of course, the "basal ganglia" in this view refers to the portion of the basal ganglia that receives projections from neocortex. One kind of stimulus–response (S–R) learning that has been used in monkeys is called conditional motor learning or the arbitrary visuomotor association task.

In the arbitrary visuomotor association task, the monkeys learned, by trial and error, that a visual stimulus instructs a given action (Murray & Wise, 1996). For the results illustrated in Fig. 10, responses consisted of forelimb movements made with a joystick. Monkeys were seated in a primate chair in front of a color monitor and a single visual stimulus on the screen instructed the monkey what actions to make on each trial. Monkeys always learned a set of three problems simultaneously; each of three stimuli in a set instructed one and only one action. For example, stimulus A might instruct the monkey to make a forelimb movement to the left; stimulus B to the right, and stimulus C towards the monkey. The two panels on the left side of Fig. 10 show the reduction in percent error as monkeys learn these kinds of problems. The solid lines show the mean performance before bilateral aspiration removal of either the hippocampal formation (top) or amygdala (bottom) and the dashed lines show performance after the surgery. Before the surgery, the monkeys learned the arbitrary visuomotor associations impressively fast; after ~8 trials per problem (roughly 25 trials total), they had mastered all three of the concurrently presented associations. Whereas removal of the hippocampal formation severely disrupted the acquisition of arbitrary mapping problems, amygdala lesions had no effect. Similar to the results mentioned earlier in this section, addition of an amygdala removal to a pre-existing hippocampal lesion had no further effect. The two panels on the right side of Fig. 10 show that the same surgeries had no effect on the

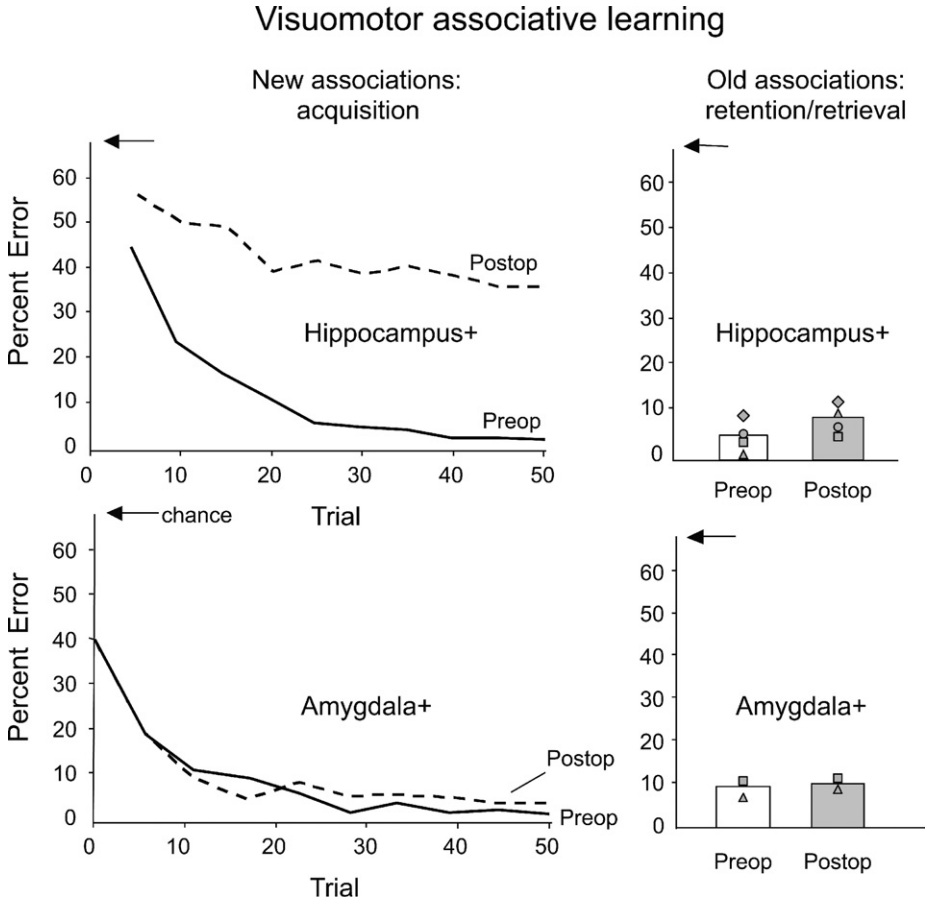


Fig. 10. Lesions of the hippocampus cause deficits in S–R learning (top left), but not in retention or retrieval of well learned S–R associations (top right). Lesions of the amygdala cause deficits in neither learning (bottom left) nor retention (bottom right). Left side: mean percent error over 50 acquisition trials. Data were averaged over 40 three-problem sets. Right side: mean percent error averaged over a block of 50 trials assessing retention of preoperatively learned problems. Bars show the group mean and symbols show the scores of individual monkeys. Data from Murray and Wise (1996). *Abbreviations:* Preop, data gathered before surgery; Postop, data gathered after surgery. Hippocampus+, monkeys with bilateral aspiration lesions of the hippocampus plus underlying parahippocampal cortex; Amygdala+, monkeys with bilateral aspiration lesions of the amygdala plus underlying cortex.

retention and retrieval of preoperatively learned problems. More recent work has shown that the fornix contributes to normal rates of learning both spatial (Rupniak & Gaffan, 1987) and nonspatial (Brasted, Bussey, Murray, & Wise, 2003) versions of this S–R learning task. Although the contribution of perirhinal cortex has not yet been assessed, these results provide further evidence for a division of labor among MTL structures.

4.4. Stimulus–reward associations

A further division of labor within the MTL can be demonstrated with the reinforcer devaluation task, a measure of stimulus–reward association. The reinforcer devaluation task requires monkeys to discriminate objects, to link objects with a representation of the current value of the food, and to use those associations to guide response selection. It is thought that this task probes the ability of monkeys to use objects to predict the outcome of an action and thereby choose appropriately. There are two phases of these experiments. In the first, monkeys are familiarized with a large number of objects, some of which are associated with one type of food, say, a fruit snack, and others with another type of food, say, a peanut. In the second phase of the experiment, consisting of four critical sessions, the monkeys are required to choose between these two classes of objects. On these trials, the two types of objects are pitted against one another, and both overlie the appropriate food. In two critical sessions, monkeys' baseline choices of objects are scored. Two other sessions are preceded by pre-feeding with one of these two foods in a procedure intended to devalue that food. Monkeys choices of either food-1 or food-2 associated objects are again scored. Under these conditions, normal monkeys shift their responding away from baseline: They avoid choosing objects that cover the now devalued food.

The measure of interest is the "difference score." As shown in Fig. 11, control monkeys do a good job of adjusting their responses; they generally avoid displacing objects that overlie the sated food. By contrast, monkeys with bilateral excitotoxic lesions of the amygdala show much less of this tendency (Malkova et al., 1997), as do monkey with disconnections between the orbitofrontal cortex and the amygdala (Baxter, Parker, Lindner, Izquierdo, & Murray, 2000). Preliminary data (Chudasama & Murray, 2004) indicate that neither perirhinal cortex lesions nor selective hippocampal lesions impair performance on this task (see also Thornton, Malkova, & Murray, 1998). Thus, the amygdala, but not the perirhinal cortex or the hippocampus, is essential for linking objects with the current value of food reinforcers. This finding is not what one would expect from viewing the MTL as a unitary functional system.

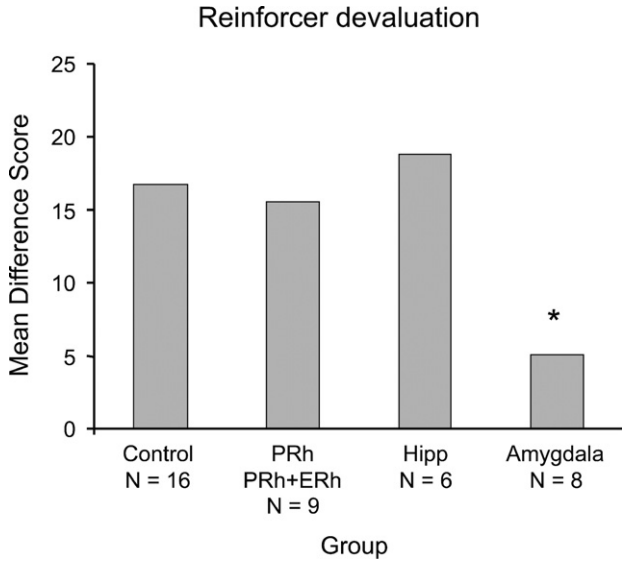


Fig. 11. The effects of brain lesions on reinforcer devaluation effects. The amygdala, not the hippocampus or rhinal cortex, is essential for linking objects with the current value of food reinforcers. *Abbreviations:* Amygdala, monkeys with selective, bilateral excitotoxic amygdala lesions; Control: unoperated control monkeys; Hipp, monkeys with selective, bilateral, excitotoxic hippocampal lesions; PRh, monkeys with bilateral aspiration lesions of the perirhinal cortex ($N = 4$); PRh + ERh, monkeys with combined, bilateral aspiration ($N = 2$) or excitotoxic ($N = 3$) lesions of the perirhinal and entorhinal cortex.

5. Beyond balkanization

Not only is the view that the MTL is a "thing" difficult to maintain, but the functional homogeneity of some of its components is also in doubt. Some studies report dissociations of function *within* the hippocampus. For example, lesions of the dorsal (septal) but not the ventral (temporal) hippocampus disrupt spatial memory tasks and, conversely, lesions of the ventral but not the dorsal portion of the hippocampus disrupt rats ability to respond appropriately in conditions of increased anxiety (Bannerman et al., 2002, 2003; Kjelstrup et al., 2002). There are also a handful of reports showing a dissociation of function within the amygdala, which, given the structure of the amygdala, should come as no surprise. For example, the basolateral nuclei of the amygdala, but not the central nucleus, mediate reinforcer devaluation effects in rats (Hatfield, Han, Conley, Gallagher, & Holland, 1996). In addition, the central nucleus of the amygdala, but not the basolateral nuclei, contribute importantly to certain kinds of Pavlovian conditioning, and, conversely, the basolateral amygdala but not the central amygdala contribute to certain kinds of instrumental responses (Killcross, Robbins, & Everitt, 1997; Parkinson, Robbins, & Everitt, 2000). These data also demonstrate the diversity of function within the MTL and violate the reification theory at a yet more fundamental level than the data reviewed in Section 4.

6. Summary and conclusions

Table 4 summarizes key results reviewed in Section 4. Taken together, the findings present a strong case in favor of the balkanization theory; there appears to be a marked division of labor among the various parts of the MTL. The reification theory holds that each component of a "thing" called the MTL provides, more or less equivalently, part of the neural mechanism for declarative memory. Table 5 shows its predictions: Large combination lesions, which include most or all of the MTL (right column), should yield greater deficits than lesions of any one or two of its components. Furthermore, based on a presumed correspondence between experimental tasks and cognitive systems, MTL lesions should impair declarative memory, but not either perception or procedural memory, the latter defined by some to include all stimulus–response (S–R) memory. Table 6 shows some of the empirical results from primate neuropsychology, which accord very poorly with this version of the theory. The reification theory is attractive, it is parsimonious, it is extraordinarily popular, and it is wrong.

Table 4
Selected findings from neuropsychology

	A	H	PRh
DNMS, feature ambiguity tasks	–	Better	+ + +
Reinforcer devaluation	+ + +	–	–
Arbitrary visuomotor associations	–	+ + +	

Data are from several sources (Bussey et al., 2002; Bussey et al., 2003; Chudasama & Murray, 2004; Malkova et al., 1997; Murray & Mishkin, 1998; Murray & Wise, 1996; Saksida et al., 2003). *Abbreviations:* A, amygdala lesions; DNMS, the delayed nonmatching-to-sample task; H, hippocampal lesions; PRh, perirhinal cortex lesions; +++, severe deficit; –, no deficit; better, higher level of performance compared to a control group.

In challenging the reification theory, experts such as Gaffan (2002) have presented what we call the balkanization theory. According to this idea, there is nothing special about the MTL or its components. The severe, selective amnesia that results from damage to the MTL is held to be a consequence of the peculiar geometry of the primate brain, which funnels essential groups of axons through a tight spot and in so doing renders them susceptible to concurrent damage that has catastrophic effects on declarative memory. The empirical psychological evidence presented here and by Gaffan (2002) supports the balkanization theory (Tables 4 and 6). But, in marked contrast to the reification theory, the balkanization theory is ugly, it lacks parsimony, and it is bound to be unpopular. The evidence lines up behind the balkanization theory, but we believe that it, too, misses something important.

The balkanization theory holds that there is nothing really special about the MTL, that each part plays some specialized information-processing function much like other parts of the cerebral cortex. But there *is* something special about the MTL. Alone among the cerebral lobes, it contains large tracts of allocortex. The hippocampus is the most prominent among these cortical areas, but there are several additional allocortical areas in and near the amygdala. The cortical parts of the amygdala and adjacent cortical fields appear to be caudal extensions of the piriform cortex and, although their functions remain

Table 5
Predictions of the reification theory

System	Task	PHC	H	PRh + ERh	MTL combination lesions
Declarative memory	DNMS	+	+	+	+ + +
Declarative memory	Object–place association	+	+	+	+ + +
Declarative memory	Fast discrimination learning (single pairs)	+	+	+	+ + +
Perception	Slow discrimination learning (concurrent pairs)	–	–	–	–
Procedural memory	Stimulus–response (S–R) learning	–	–	–	–

Abbreviations: DNMS, the delayed nonmatching-to-sample task; H, hippocampus or fornix lesions; MTL, medial temporal lobe lesions that combine two or more components of the MTL; PHC, parahippocampal cortex lesions; PRh + ERh, combined lesions of the perirhinal and entorhinal cortex; +, mild deficit; +++, severe deficit; –, no deficit.

Table 6
Empirical neuropsychological findings relevant to the reification theory

System	Task	PHC	H	PRh + ERh	MTL
Declarative memory or not	DNMS	–	±	+++	+ + +
Declarative memory or not	Object–place association	+ + +	–		
Declarative memory or not	Fast discrimination learning (low feature ambiguity)		–	–	
Perception or more	Slow discrimination learning (high feature ambiguity)		Better	+++	
Procedural memory or not	Stimulus–response (S–R) learning		+++		+++

Abbreviations: DNMS, the delayed nonmatching-to-sample task; H, hippocampus or fornix lesions; MTL, medial temporal lobe lesions that combine two or more of the components of the MTL; PHC, parahippocampal cortex lesions; PRh + ERh, combined lesions of the perirhinal and entorhinal cortex; +, mild deficit; +++, severe deficit; –, no deficit; better, performance better than a matched control group.

enigmatic, some neuroanatomical work suggests that they share a close association with the autonomic nervous system (Westerhaus & Loewy, 2001) and the hypothalamus (Swanson, 2000). If one accepts the conclusions of Swanson and Puelles and their colleagues, outlined in Section 3, the MTL also contains small, extremely caudal parts of the striatum and, for what it is worth, the claustrum, too. Perhaps these ideas will contribute to an improved understanding of the "thing" called the MTL in primate brains—some day. That day has not come, at least not for us, and we make no attempt to develop a grand synthesis or alternative theory here.

Were we to attempt to go farther, which we will not, we might point out that all of these allocortical areas and their associated parts of the striatum and pallidum have long evolutionary histories, perhaps stretching back to some of our most distant vertebrate ancestors. We might speculate that the MTL is special because of the long history of its allocortical components, because of some role in the behaviors most fundamental to the life of vertebrates, or because of a role in certain instincts and the behaviors built most directly on instincts.

We feel, however, that such speculation would break the pledge that we made at the beginning of this presentation. We began this review with the promise that we would attempt to convey two (and only two) take-home messages: (1) Any theory that attempts to distinguish the functions of one "thing" called the MTL and another "thing" called the basal ganglia should take into account all of the latter's components (as illustrated in Fig. 4), not merely those that have become most prominent in mammalian brains because of their relationship with the neocortex. In the context of Fig. 5, we believe that row-wise thinking (Fig. 5B) will prove to be more useful than column-wise thinking (Fig. 5A). And (2) the MTL is not a "thing" at all. "It" is a collection of functionally disparate structures that each contribute to memory, perception, and response selection in a specialized way (Table 4):

- the amygdala (also not a thing)—not the hippocampus and not the perirhinal cortex—links objects with the current value of food reinforcers and thus contributes to response selection;
- the perirhinal cortex processes, represents, and stores object features, it associates inputs within and across sensory modalities, and it does so in the service of both perception and memory; the perirhinal and entorhinal cortex—not the hippocampus and not the amygdala—underlie the memory of objects as measured by the DNMS task; and
- the hippocampal system (including the fornix)—not the amygdala—contributes to the acquisition of arbitrary S–R associations ("habits," according to some authorities), whether spatial or nonspatial in nature.

7. Epilogue

We stated in Section 1 that we hoped it would be helpful to change the question from "What does the MTL do?" to those posed in our title. But we have made no attempt to answer those questions yet. So: What, if anything, *is* the MTL? How can the amygdala be part of the MTL if there is no such "thing" as the MTL or the amygdala? These questions are difficult to answer because the phylogenetic and ontogenetic processes underlying the fantastic expansion of the neocortex have distorted the relationships among structures in the forebrain almost beyond recognition. It is easy to think of the MTL's components and the basal forebrain as separate building blocks that abut each other in some arbitrary way, as if they were boxes like those in Fig. 1 that could be rearranged to suit the heuristic requirements of a given theory, a course of instruction, or some other cultural construct. But the anatomical arrangement of structures in the forebrain results from the evolutionary and embryological processes that put them there: The structures that end up in the MTL of primates result from that history. Notwithstanding some interesting patterns of cell migration during development, the telencephalon cannot stray far from the geometric relationships established in the embryonic telencephalic vesicle (Fig. 3A). The ends of the hippocampus do not detach and reconnect in some haphazard way during development. Nor do the components of the telencephalon rearrange themselves willy–nilly. The telencephalic vesicle can expand, balloon, fold, and contort beyond credible comprehension, but fundamental geometrical relationships remain. These considerations lead to our answer: The MTL of primates is what it is because a part of each of its components is located near the junction of the basal forebrain with the temporal lobe (green circle in Fig. 3A). The nuclei and cortical structures collectively called the amygdala are located there, too, and so it is reasonable to include them.

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