The Memory Labyrinth: Systems, Processes, and Boundaries

3

Robert A. Veselis

Introduction

> The business of life is the acquisition of memories. Carson (Downton Abbey S4E3)

This topical quote was continued as "in the end that's all there is." In a sense this highlights how memory makes us uniquely human. As the human mind is the most complex creation in the universe, it stands to reason that memory embodies to a large extent this complexity. When memory fails in the end for some of us, a large portion of our being human also fails. In dementia some basic forms of memory do still exist and function, and functioning begins to rely more and more on stereotypical unconscious rather than recent autobiographical memories. During our whole lives unconscious memories allow us to function in an ever changing world by, for instance, jumping at a loud (potentially dangerous) noise, moving a piece of food to our mouth, or choosing a candy for unknown reasons from among dozens available. These unconscious memories seem to be implemented in the very core of our brains, and the question of whether consciousness can exist in the absence of memories is one of terminology. Certainly, conscious memories can be absent in the presence of consciousness, but a sine qua non of consciousness is the presence of working memory (memory of the here and now, even if the here and now is never remembered).

From this brief introduction, one can see memory is a complex phenomenon, or more accurately closely interrelated phenomena [1–3]. There are multiple memory systems, the classical division being between conscious and unconscious memory processes, which are supported by different, but not necessarily exclusive neurobiologic processes [4–6]. As will become clear throughout this chapter, the boundaries between these divisions are not as simple as many classification systems (taxonomies) imply. Largely this is a result of trying, as it were, to put memory into a box and it won't fit!

What is a memory? At the most basic level it is a rearrangement of our brains at the synaptic level [7, 8]. Memory is a process that produces a brain different from what it was before, that difference being the memory. Synaptic rearrangement does not occur instantaneously, and the sum of the processes needed to complete these changes is termed "consolidation" [9]. As we can attest to from our daily lives, memory is not a static entity and is constantly evolving over time, although the rate of change may be different over different temporal epochs. Old memories can be re-remembered, and the term re-consolidation describes the process of recalling a memory and then storing a slightly different version. In fact, events similar to this occur every night during sleep, where the neural records of events from the previous day are massaged by waves of the oscillatory activities of the sleeping brain [10–12]. In fact, we are now in an age where it might be possible to manipulate memories at will, the implications of such actions being quite profound and still quite unclear [13].

How does one determine if synaptic changes have occurred? Not being able to visualize synaptic changes in real time (until recently, but with totally impractical methods), a proxy is needed [14]. In the end, the only way one can determine if a memory is present is by observing a change in behavior which is in some way related to the creation of that memory. In this sense memory is a behavior, and therein lies the source of much controversy when memory is discussed. The observations of memory related behaviors are largely undisputed. Everyone agrees, for example, that the reaction time to a stimulus in a particular paradigm has decreased, or that recognition with a given degree of confidence has occurred. However, it is frequently the case that very differing opinions are offered as to how to

R.A. Veselis, MD (✉)
Anesthesiology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, USA
e-mail: veselisr@mskcc.org

A.R. Absalom, K.P. Mason (eds.), *Total Intravenous Anesthesia and Target Controlled Infusions*,
DOI 10.1007/978-3-319-47609-4_3

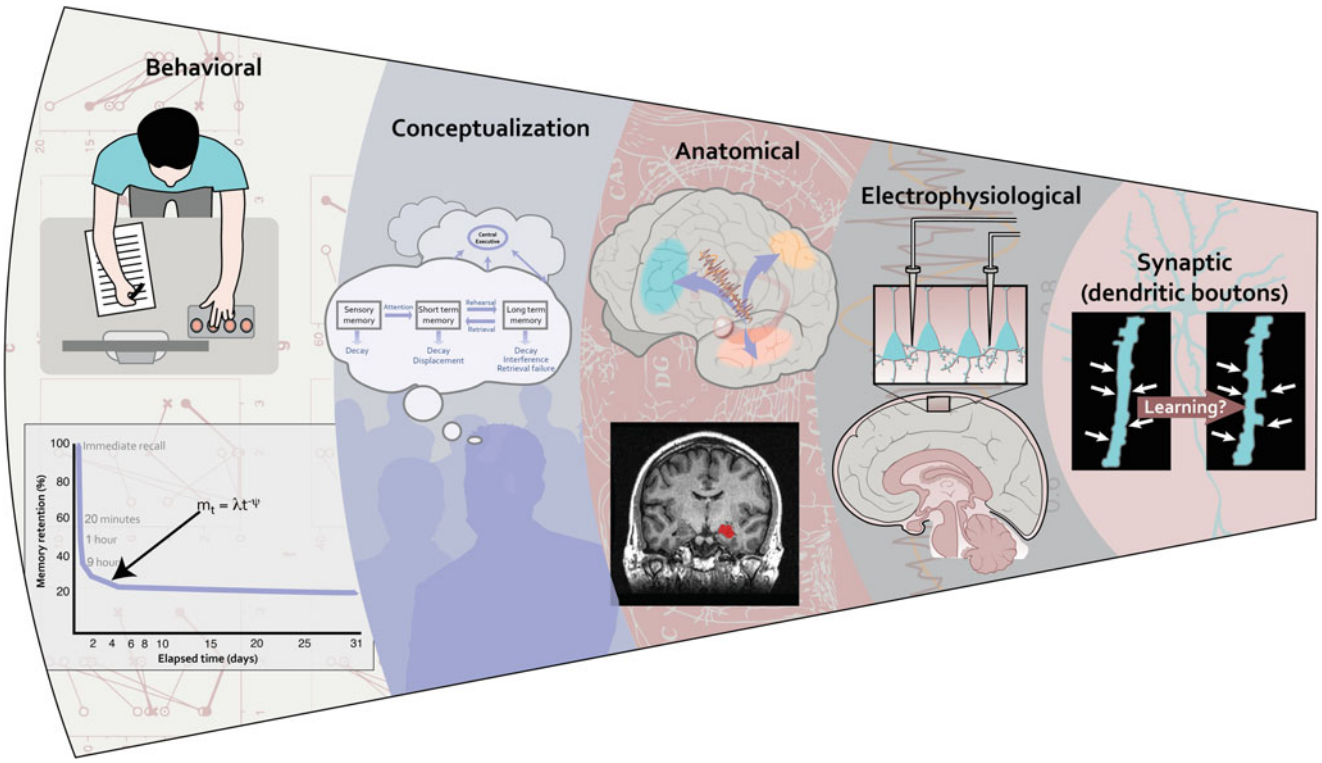

Fig. 3.1 The many levels of memory. Memory can be understood at many different levels, from behavioral changes to synaptic modifications in neurons. Conceptualizations of memory begin with careful behavioral observations in humans or animals, where specific parameters are changed (e.g., time between encoding and recognition), and changes in behavior are measured. A conceptual construct can be created to explain these observations, such as short (working) and long term memory systems. These conceptualizations are then related to underlying neurobiologic mechanisms in terms of anatomy, electrophysiology, and molecular mechanisms [and in some instances physical principles (e.g., quantum mechanics)]. The great challenge is to link changes in, for example, phase changes in oscillatory activity that influences synapse formation with something as complex as recognition memory

these behaviors are explained. Behind every behavioral result, there stands a conceptualization of a memory system, or set of memory systems which allows one to explain why a given behavior resulted [15] (Fig. 3.1, left-most sections).

The best conceptualizations are those that allow one to predict ahead of time what change in behavior will occur under a given set of circumstances [16]. Careful study of behavior under these circumstances will allow more solid acceptance, or lead to more degradation of a given conceptualization. Frequently predictions of a model are tested in a patient with a known brain lesion, e.g. one that affects procedural (e.g., mirror drawing), but not long term memory. Ideally a matching study is done in a patient with an opposite type of lesion, e.g. a patient with a deficit in long term, but not procedural memory [17, 18]. A similar dissociation can be demonstrated between short and long term memory stores [19, 20]. Dissociability along these lines provides strong support of separate memory processes, but one problem is that it may be very difficult to locate a patient with a specific enough lesion that clearly interferes with a single memory function. In this iterative process conceptualizations are verified or refuted, with new and improved ones being a result. The introduction to a conference on episodic memory written by Baddeley is an excellent example of how this process unfolds [21]. It should be noted that in the 2010s we are still engaged in these iterative processes. Thus, concepts of memory are continually evolving, and certain key ideas are as hotly debated as cherished political beliefs. To best understand memory, one needs to be somewhat familiar with the unfolding of conceptualizations (a.k.a. taxonomies) of memory over time. In this chapter as well, I will describe what is known of anesthetic induced manipulation of memory, though knowledge is still at a somewhat primitive stage.

A History of the Taxonomy of Memory

The noteworthy idea that memory was more than one entity was proposed only in the last half of the last century, really not that long ago. Though in 1949 Hebb presciently suggested a distinction between memory processes with short term memory being defined as evanescent electrical

activity, with long term memory being consisting of more permanent neurochemical changes, it was Atkinson and Shiffrin who are most credited with fleshing out the concept of these two major forms of memory [22]. Before then, it was still quite controversial whether memory could be regarded as anything by a unitary process [23]. This argument is eerily similar to the current controversy regarding the nature of recognition in conscious memory, which will be detailed later in this chapter. As usual in these situations, the behaviors which lead to conceptualization of short vs long term memory were well accepted. The now famous 7 ± 2 items capacity of short term memory was established in the 1950s. This was the amount of material that could be recalled immediately after presentation [24, 25]. Fortunately for many generations, telephone numbers fit this bill, especially as alphabetic prefix codes were used. One could easily remember a telephone number after hearing it once. In fact, songs have been written about this (PEnnsylvannia 6-5000, Glen Miller orchestra[1]). Atkinson and Shiffrin (among others) wanted to understand and detail mechanisms to explain this observation. A major insight was to postulate a short term memory store of limited capacity. When the ninth item comes along, item one is pushed out. The interaction of a short term store with recent items in long term memory could explain more complex behaviors, such as the serial position effect, where items from a long (greater than ten item) list are recognized with a U shaped probability [26]. Initial and last items are likely to be remembered better, as items from the start of the list are likely to be rehearsed and incidentally encoded into long term memory, whereas recent items are still present in working memory and easily recalled (more detailed explanations are more complicated, the serial position effect is a whole field of study) [27]. A few decades later, after numerous behavioral/conceptual iterations, short term memory was conceptualized as working memory, itself consisting of different sub-components. Each component was a conceptualization that could explain an associated behavioral or set of behavioral observations. Predictions of previous models broke down when more closely examined, or in patients with specific neurologic lesions. Baddeley improved the concept of short term memory by defining separable components collectively termed working memory [28] (Fig. 3.2). These conceptualizations in turn led to more detailed neurocomputational and neurobiologic conceptualizations that propose how cognitive conceptualizations are instantiated in the brain. It is easy to see how memory can be considered at different scales representative of multiple layers that interact with each other (Fig. 3.1, all sections). For example, a well-accepted neurobiologic

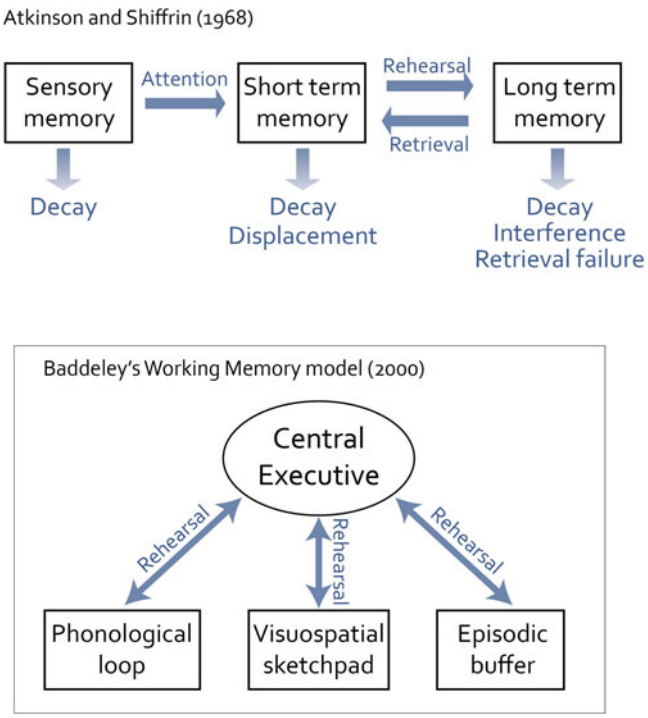

Fig. 3.2 Refinement of conceptualizations over time: The figure provides a simple illustration of how a basic conceptualization, of short (STM) and long term memory (LTM), can become more elaborate as more detailed behavioral observations are subject to analysis. A number of observations, such as the inability to remember beyond 7 ± 2 items when rehearsal was prevented, lead to the famous dual store conceptualization, as described by Atkinson and Shiffrin in the 1960s. However, observations predicted by this model (that patients with impaired STM should have broad deficits in LTM) were not actually observed, and a more refined conceptualization of Baddeley resulted, that of working memory with multiple components handling different types of input (phonologic, visuospatial, semantic). It should be remembered that such conceptual elaborations of memory systems are still occurring

conceptualization of working memory is a process embodied in the oscillatory activity of the brain, which provides a capacity as large as the ratio of gamma to theta frequencies (roughly), which happen to be on the order of 7–9 to 1 [29]. Thus, starting with very basic properties of neurons, modeling small world neuronal interactions can serve to explain an observed behavior much removed from this level of detail [30]. Such a reductionist approach lends solid credence to the observation that working memory is fleeting. As mentioned before, a critical requirement of consciousness is working memory, as to be conscious is to be aware of the "here and now," instantiated as working memory [31, 32].

After being processed in working memory, some information does become long term memory. LTM embodies Carson's comments on our being human, as working memory is so evanescent. Not surprisingly the more closely we examine long term memory the more we appreciate that it itself is incredibly complex. As with the dichotomy between

[1] http://en.wikipedia.org/wiki/PEnnsylvania_6-5000.

short and long term memory, conceptualizations of LTM began as a dichotomy between conscious and unconscious memory [33]. This dichotomy was best illustrated in the 1950s by the world's most famous neurologic case, H. M. [34]. He was one of a series of seven patients reported by Scoville and Milner describing a peculiar memory deficit after therapeutic surgery to cure intractable epilepsy. Surgery such as this may seem to be a radical approach today, but the concept was founded on the observation from a decade before that if a diseased portion of the brain was removed, this would "liberate" normal functioning brain no longer inhibited by the scarred brain tissue [35]. Interestingly, to this day a similar approach with appropriate refinements still seems to be the best option in some situations, such as drug resistant epilepsy arising from discrete scar tissue in the temporal lobe [36]. With improved surgical methods, seizure mapping, and understanding of neurobiologic mechanisms resection does result in some improvement in specific memory abilities, harkening back to the original work of Hebb and Penfield [37].

As illustrated by the Scoville case series, unexpected consequences may be more important for the advancement of science than dreamed of. After surgical treatment for epilepsy, it did seem that an almost magic cure was found. Before surgery, the patient was essentially incapacitated, sometimes to the point of not being able to leave the house because of relentless seizures or intoxication of too high doses of barbiturates to treat those seizures. After surgery a virtually normal life resulted. Detailed descriptions of the peculiar memory impairment associated with this type of surgery, one that is able to be reproduced in the surgical theater when a patient is given a benzodiazepine, led to eventual knowledge of the key role of the hippocampus in conscious memory. Similarly, one will note that a patient undergoing sedation with light doses of diazepam, midazolam, ketamine, or propofol frequently keeps asking the same question. This is a predictable behavior in patients receiving light doses of these drugs, and results from the fact that patients can't remember the answer to their repetitive questions. It should be noted that after the case reports of Scolville and Milner, it was decades before there was enough evidence to clearly point to the hippocampus as the seat of conscious memory [38]. The reason it took so long to confirm this relationship was that in the original case series not only was the hippocampus removed (bilaterally) during surgery, but the resection also included a complex set of structures closely related to the hippocampus which also resided in the medial temporal lobe [5]. It took many years to determine how these structures were interconnected and how they interacted. The Scolville and Milner case series really re-invigorated the conceptualization of memory systems as being embodied in certain structures of the brain. Not surprisingly a huge amount of basic research on memory focused on the neuronal architecture of the hippocampus, and related structures [39].

Animals are valuable to study memory, as one can control conditions very closely, manipulate genes, record from individual (giant) neurons, and obtain really fine grained data. For example, a prototypical system is the Aplysia (sea snail/slug), which is a vehicle to study reflex and simple behaviors, such as classical (reflex) and operant (e.g., eating) conditioning. These forms of memory are stereotypical, and though much is known about them, how these systems influence memory processes in humans is still murky. Much of the classical taxonomy of memory relates to these stereotypical, unconscious memory systems. Included in these behaviors are priming, skills and habits, classic conditioning and non-associative behaviors [33]. From the perspective of this chapter, priming is the most important, as it is the type of memory most sought after when studies look for learning during anesthesia. Priming is the preferential response to a previously experienced stimulus, one that is not consciously remembered. Indirect tests to detect these memories must be used, as they are not consciously accessible. The most common task used is word stem completion, where a portion of the stimulus word is presented, and the rate of completion using previously presented words (during anesthesia) is compared with a control list [40]. Habits and skills are stereotypical behaviors that are initially conscious memories that through repetition are incorporated into motor circuits as unconscious memories. Being stereotypical, even small changes in pattern requires new conscious learning (the bane of pianists who initially learn an incorrect note in a passage, for example). Pavlovian conditioning is best known to humans (and maybe dogs) as what occurs when smelling bacon. Non-associative learning embodies habituation or sensitization to a repetitive non-relevant or harmful stimulus, respectively. More complex memories, particularly in animal models, may be difficult to categorize as being conscious or unconscious if the organism cannot provide insight into the experience. For example, in rats a more complex memory is visual object recognition, where a rat will explore a novel object in preference to an object previously seen before. Though some literature equates visual object recognition memory to conscious memory in humans, it seems that the memory systems mediating object recognition may best be related in humans as unconscious memory [41]. The divide between animal neurobiology and human memory becomes wider as more complex memory is considered. In the case of visual object recognition memory, the hippocampus was thought to play a vital role. Hippocampal involvement is considered as a proxy for conscious memory in animal models. A number of studies showed that animals with hippocampal lesions were impaired in object recognition memory. However, when memory paradigms were carefully constructed to not contain spatial cues, it turned out that

hippocampal lesions made no difference in object recognition memory. Thus the initial lesion studies were contaminated by subtle environmental cues, highlighting the sensitivity of memory studies to confounding factors. The closest parallel between animal object recognition memory and human memory may be face recognition, which recently has been shown to activate parahippocampal structures [42].

The largest divide between lower animal models and humans occurs in the case of conscious memory, which is the memory referred to by Carson [43]. This is what most people think of as "memory," and is incredibly complex and somewhat hard to pin down, especially in animal models. The history of taxonomy starts with declarative memory, which is a memory we can (consciously) declare we have. Further characterization of conscious memory led to the realization that these memories really occur in a place and in particular a time, best described as episodic memories, episodes that are like frames in a film strip (which in fact is a paradigm used to study this form of memory) [44]. The closer one considers and investigates episodic memory, the more complex it becomes. For example, there is a distinct sense of knowing oneself in episodes of conscious memory, thus best characterized as "autonoetic" memories. In addition, one can envision one's self travelling through time, most critically, into the future (what will happen if I lie about what I did last night . . .) [45]. It will be very hard to convincingly demonstrate these qualities of conscious memories in animal models. In fact, some authorities do not think animals possess conscious memory as we do, and that even scientists anthropomorphize their pets. Complex paradigms used in animals are claimed to be representative of higher forms of conscious memory, but other experts consider these memories to be, at best, "episodic like" [46–48]. Thus, even though animal models may provide copious and invaluable information about memory, the ultimate discovery of how human memory works will require study of humans themselves. It will always be a conundrum of how to relate memory from one species to another. Again the observed behaviors in a particular animal model are undisputed, it is the interpretation of how these results relate to human memory that is the source of controversy.

As regards conscious memory, the safest correlate of "conscious memory" in animals is probably spatial memory, which is indisputably mediated by the hippocampus [49–51]. Common paradigms to study this form of memory are paradigms such as the radial maze or the Morris water maze, where the animal depends on extraneous spatial cues to remember previously explored avenues. In fact, the discovery of hippocampal place cells/fields revolutionized concepts of the neurobiology of conscious memory [52, 53]. The divide between animal and human hippocampal neurobiology has been considerably diminished using sophisticated signal analysis methods in epilepsy patients with implanted electrodes, for example [54].

Most readers are probably familiar with the classic taxonomy of memory, which is a distillation of many decades of research founded on centuries of behavioral observations. This classic classification deserves a Figure as a historical starting point (Fig. 3.3). Currently, a

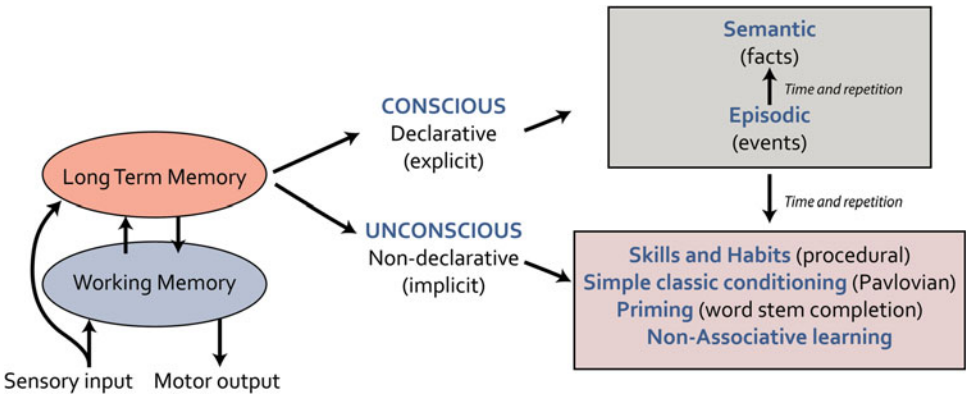

Fig. 3.3 A "classic" conceptualization of human memory systems. Long term memory is classified into various components in Squire's model [55], and is based on much animal work as well as observations in patient lesion cases. These concepts arose after the report of impaired memory in a series of neurologic cases (case HM, reported by Scoville and Milner in 1957), following surgery in the medial temporal lobes. Classically, long term memory was considered in large part as a static entity, which can be classified according to features of the memory (e.g., conscious access vs. unconscious influence). A large body of multiple line evidence obtained over a 30-year period revealed that the hippocampus was essential for the formation of conscious, episodic memory explaining the observations of Scoville and Milner. A clue to the fact that this classification is just a starting point in understanding memory is illustrated by some "permeability" between categories. For example, at one time the knowledge that George Washington was the first president of the USA was a new and startling memory (an episodic memory), but then it became a "fact," knowledge of the world that we do not recall where and when it was learned (semantic memory). Similarly, patterned behaviors such as skating and playing a musical instrument become unconscious motor memories over time

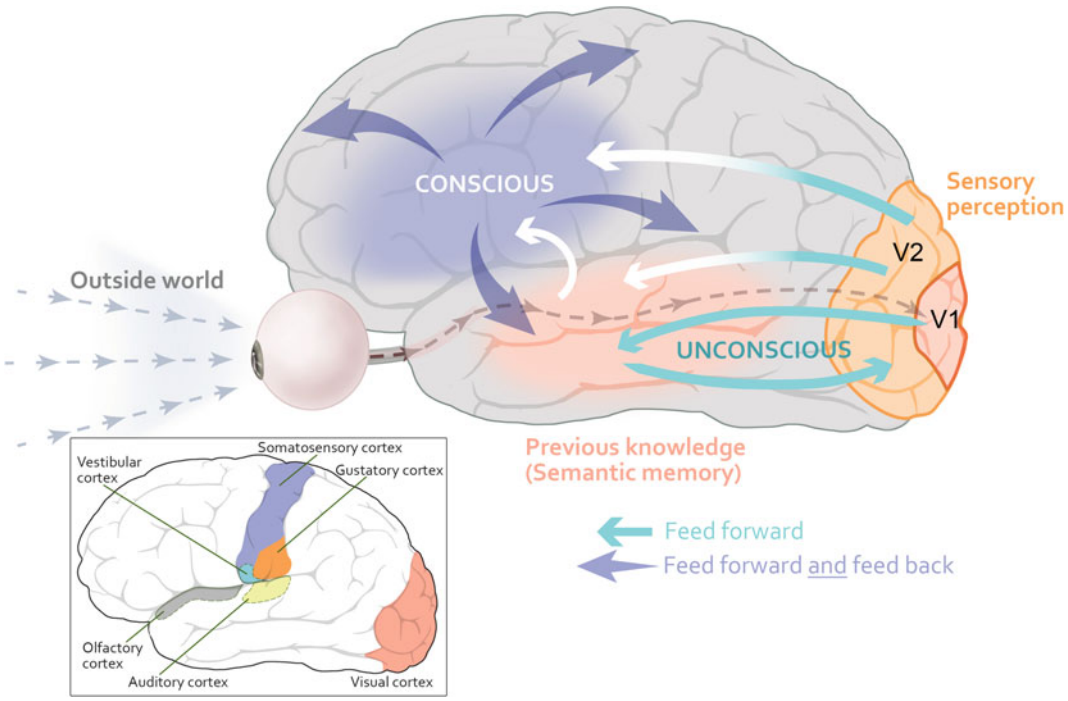

Fig. 3.4 More recent conceptualizations of memory. These conceptualizations build on the concepts presented in Fig. 3.3 using a foundation of neuroanatomical relationships. Memory systems are widely distributed, and interact with each other in somewhat flexible fashions. Those closest to the environment (sensory regions) are "low level" systems which are the most easily understood on a basic physiologic level, and most likely embody portions of unconscious memories. Higher level systems that embody conscious memory likely depend on network activity and distributed processes, though all systems interact with each other in complex fashions to not only subserve memory function, but also consciousness. Higher level interactions are more sensitive to anesthetic effects, and low level systems may still be functional in certain situations during anesthesia, wherein unconscious memories may be formed. However, these memories may simply be perceptual (sensory) priming memories where an enhanced physiologic response occurs to a re-experience of the stimulus. At our current state of knowledge of neurobiology, these sensory memories formed during anesthesia would require the interaction of sensory input regions (e.g., V1 for visual, A1 for auditory) with other multiple brain regions (likely in the medial temporal lobe), with any resulting sensory memories residing in peri-sensory brain regions (V2 or A2). Pathways for sensory processing are shown for the visual modality for clarity, the same principles would apply to auditory or olfactory sensory systems in their respective brain regions

major shift in conceptualization of memory is occurring where taxonomy is changing in nature from a static classification of memory systems to conceptualizations that incorporate information flow from the outside (or inside) world through stages of processing to a conscious or unconscious memory [56] (Fig. 3.4). Information transfer and processing become important components of these conceptualizations, which now include the malleability of memory itself (false memories, eye witness memories, post-traumatic memories, etc.) [57]. Careful readers of the mechanisms of anesthesia literature will no doubt appreciate a close resemblance to similar concepts of consciousness, and the progression of information from sensory and internal sources into a percept that one is consciously aware of [58, 59]. In fact, this is likely no co-incidence, as neurobiology is more than likely parsimonious in implementing solutions for similar problems, be it consciousness, working memory, or long term memory.

A Useful Conceptualization of Memory

One needs to have a working conceptualization of memory that incorporates bits and pieces of different models to avoid getting hopelessly lost. The classic taxonomy is useful in terms of nomenclature, and will be utilized as such. As mentioned, the current direction of memory research is in terms of information processing, and it is best to relate these concepts to the classic nomenclature as a starting point. To simplify, I will only consider information from the outside world, though the same principles, but not necessarily specifics, can be applied to the inner, dreaming world [58, 60]. To begin with, let us consider how a picture frame from the film of our lives becomes a memory, and more. But before this, one should become familiar with the basic construct of a memory study.

Memory as a Behavior: The Ebbinghausen Paradigm, or More Simply, Study-Test Paradigm

About 150 years ago a psychologist, Hermann Ebbinghaus, was interested in quantifying memory. We all know that the most common fate of memory is that it is forgotten [61]. This is a very fortunate state of affairs, for if you pay attention to all the stimuli that are processed in a single day, and then think of what life would be like if you remembered each stimulus for the rest of your life, you would quickly realize you would be living a nightmare. As is common for many "life is stranger than fiction" diseases, there is the rare neurologic case that embodies a form of super-memory [62]. Such people can remember, for example, all the details of the weather on a particular date many years in the past. Not surprisingly, it does turn out that significant psychological distress accompanies such super-memory ability.

Thus, it is no surprise that historically, one might be first interested in quantifying the most basic property of memory, namely how it is lost. Ebbinghaus proceeded to do this in a systematic fashion, where given items were studied, and then recognition for these items was used to quantify memory decay over time. Almost all behavioral observations of memory, both in humans and in animals, use a study-test (encoding, recognition) paradigm, also referred to by those in the field by Ebbinghaus' name. To this day this paradigm is the only way to practically detect and measure a memory, ultimately a result of synaptic re-arrangements in the brain. Another important variable in this paradigm is the time between encoding and recognition [63]. Multiple recognition tasks can be performed, which is what Ebbinghaus did, to define memory decay (or, alternatively, improvement from repeated practice on the task) [64]. There is an almost infinite variety of paradigms available by modifying the three main elements of the study-test paradigm, those being encoding, time to recognition, and recognition. During encoding and recognition tasks, the particular instructions given, including any modification of the environment or context is crucial to interpret the results, as will be exemplified throughout this chapter. Time is the factor that is the most quantifiable, but one must be aware that it is crucially important to know what the person/animal is doing (or more accurately is instructed to do) during the time between encoding and recognition.

What Ebbinghaus quantified was that memory decays very rapidly at first, and then more slowly as time increases (Fig. 3.5a). Eventually, an autobiographical memory remains, those of episodic experiences long ago [65–67]. In closely related circumstances, probably with repeated encoding activity, an episodic experience is transformed into a fact—knowledge about the world. For instance, we know that stoves are hot, but we don't remember how that information got into our memory. This form of memory is termed semantic, a term that embodies perfectly the relatedness to the meaning of words, which is really knowledge of the world. On the other hand, memories associated with motor skills (driving a car, playing a musical instrument) becomes embodied, through repeated encoding, into a primitive (or phylogenetically old) set of neural circuits in our brain which allows automated behavior, and is a form of unconscious memory [68, 69]. But, let's turn back to episodic memory decay. Mathematical modeling of memory decay is possible, and it seems that a power decay function, as opposed to an exponential decay function, fits data the best [70, 71]. Parameters from the power function fit can, for example, quantify memory decay characteristics of common anesthetic sedatives, discussed later in this chapter [72].

Recognition memory is tested by asking the subject to perform matched encoding and recognition tasks. Often the instructions for encoding are thought of as a variation of "remember these items, for you will be asked to name them later." This is certainly a valid encoding paradigm, but more frequently incidental encoding paradigms are used, where the subject follows a relatively easy instruction that on the surface is not related to memory, such as "you will hear a series of words, push one button if the voice is female, and the other if it is male" [73]. No indication is given that the words will be incorporated into a recognition task later. The person pays attention to the task, and normally, the words presented are incorporated into memory automatically, thus the term incidental encoding. Slight modifications of task instructions, such as "push one button if the word is an object that is larger than a bread box, otherwise push the other" will activate different memory systems, and thus result in different memory performance at recognition [74]. In studies of unconscious memory, frequently the length of time of presentation or clarity of the item is varied. For example, a picture may be shown for 33, 50, and 80 ms to determine a perception threshold, and then changes in behavior are measured, those usually being reaction times to stimuli which were presented at longer and shorter time intervals than the perception threshold [75]. Shorter intervals index unconscious memory processes, whereas longer intervals index conscious memory processes. Similarly, words may be degraded by white noise to determine a perception threshold for information content.

During the time interval between encoding and recognition, the environment and instructions to the subject are crucially important. Variations include performing an "interference" task, resting comfortably, sleeping, staring at a cross hair on a computer screen, etc. All will result in differing memory performance, and one should be aware that vagueness about what actually was done during this period would confound results from that study.

There are many recognition paradigms, again with crucial differences in instructions. One main theme is that

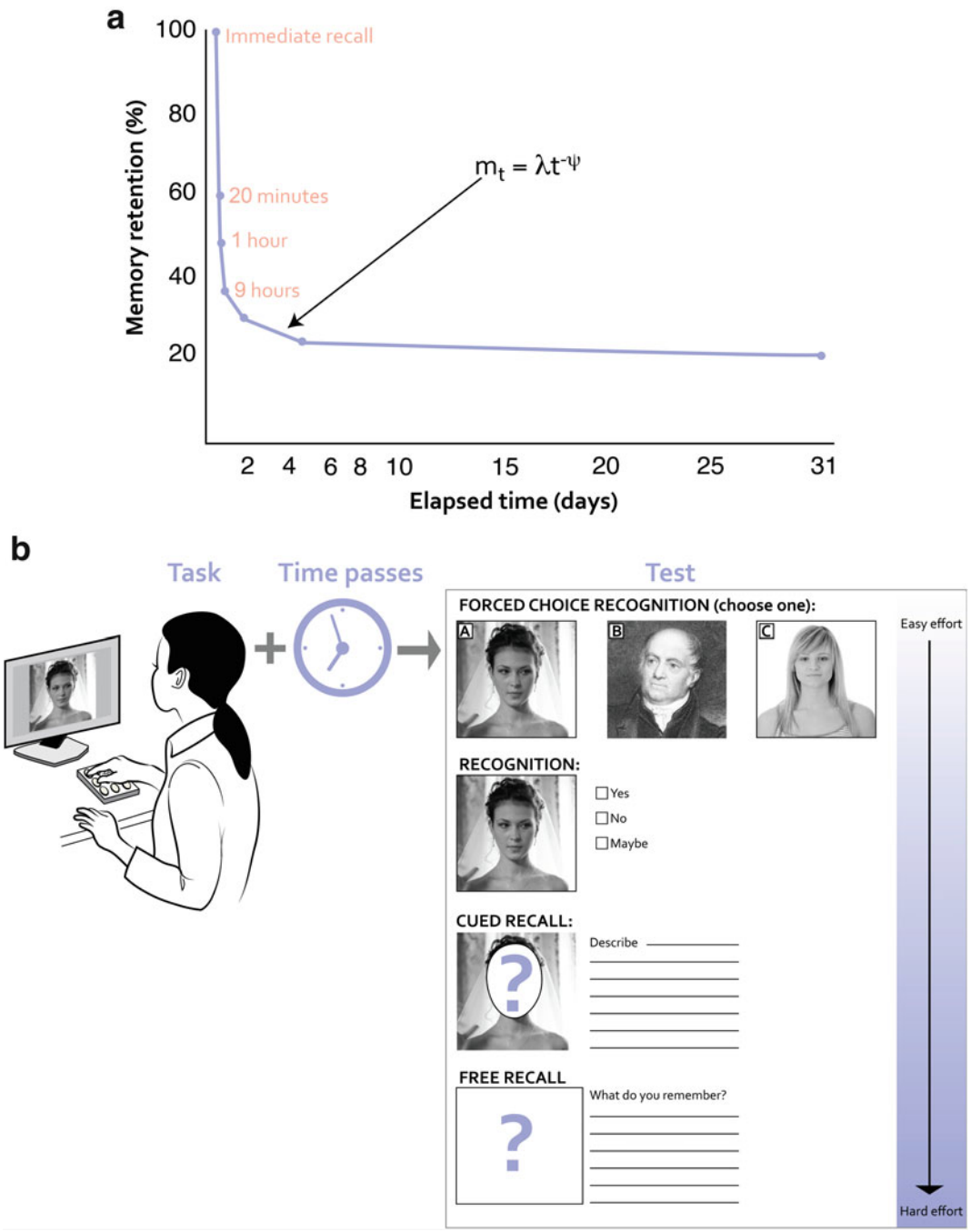

Fig. 3.5 (**a**) The fate of memories is to be forgotten. Ebbinghaus established basic observational principles to quantify memory behavior. An event (stimulus) is experienced (encoded). After a certain time, the presence of memory is tested for by a recognition task. This study-test paradigm (Ebbinghausen paradigm) revealed that most memories are forgotten over time, rapidly at first, and then more and more slowly. A power decay function (as opposed to an exponential decay function) best describes loss of memory over time. (**b**) Depending on specific parameters and instructions for encoding, recognition, etc. many variations of the study-test paradigm are possible. For example, the difficulty in accessing a memory can be varied by giving clues, providing a choice of possibilities, etc. How behavior changes with these modifications provides important insight into how memory operates, and which brain regions are involved with different aspects of memory such as attention and effort needed to retrieve a memory

recognition performance is greatly affected by the effort required to retrieve a memory. It makes sense that if you have to remember a previous item out of the blue, that would be more difficult than choosing between two items after the instruction "you have seen one of these before, which one was it?". This effect is well known, and difficulty of retrieval from hardest to easiest is illustrated by examples as follows: free recall ("what do you remember"), cued recall ("do you

remember something that looked like a car"), yes/no recognition ("have you seen this item before, yes/no"), forced choice recognition ("choose the one you have seen before from these three items"), forced choice recognition using two items (Fig. 3.5b). The degree of similarity of the lure items (items given as choices, but not previously presented) will modulate the degree of difficulty, and such variations can be used to determine a "signal strength" of the memory [76].

From these brief examples, one can appreciate the almost infinite variety of paradigms possible in the study-test format. Each small manipulation provides, hopefully, another insight into how memory works.

From Sensation to Memory: Information Flow

This section will focus on conceptualizations of information flow from the outside world into the brain where it can become a memory. These conceptualizations are embodied as distinct memory processes (encoding, storage, recognition, etc.) and are divorced from neurobiologic instantiation [15]. The reader should be aware of this distinction, even though some are closely linked (e.g., hippocampus and conscious memory). One should not get into the habit of freely substituting a neurobiologic mechanism for a conceptualization, or vice versa. Some neurobiologic underpinnings of memory behaviors will be discussed in more detail in the sections on unconscious and recognition memory.

An important differentiation in terminology common to memory and consciousness is needed, particularly for those interested in anesthetic effects on the brain. What is the correct terminology for seeing a light? Some people might say that the light is perceived, whereas others would say that it is sensed. Some would argue that perception is a more complex bit of information than sensation, that perception has some greater structure to it. In fact, in the study of consciousness, a key concept is that of a percept, a unified experience of awareness that incorporates many different threads of information. To avoid confusion, I will use the word "sense" for primary activation of sensory cortices from the outside world (e.g., primary auditory or visual cortices). Terms containing "percept" will relate to a conscious experience of an event from the outside world [31].

The first event of a potential memory is sensation, an activation of primary sensory cortices (Fig. 3.4). Most real world events activate multiple senses, but for research purposes, most stimuli stimulate a single sense. Immediate, unconscious processing occurs of the stimulus to measure basic qualities of the stimulus (e.g., intensity, orientation, frequency, color, etc.). At a very early stage, comparison with a template (a previously experienced stimulus, either at some time in the past, or in the current train of stimuli) is undertaken [77, 78]. If there is a mismatch, neuronal responses tend to be larger [79–81]. A deviant stimulus may be of interest or importance, and mechanisms come into play to devote attentional resources to the incoming stimulus (aptly named as a "bottom-up" attentional modulating process). Neurophysiologic correlates of the so-called orienting reflex can be measured, e.g. as the mismatch negativity, and can be used to study how sifting through a the constant stream of incoming information directs important details to the most relevant brain systems. As with a Christmas tree, important stimuli are collated with more and more information to elaborate what was just experienced into a conscious percept [56]. As an example, we may jump when we hear a loud noise. Auditory sensation is activated, the characteristics of the sound are automatically extracted (loud, short duration, previous match with an explosion), the flight or fight response may be activated (fear mediated memory), a motor reflex occurs (jump) before further processing occurs. Additional details may then be added, for example from the visual stream (we turn to see a broken plate on the floor). We access previous semantic knowledge (bits of porcelain from a plate, when plates break they make a loud noise) in order to make sense of what just happened. Further fear processing is stopped (it was not a bomb), we collect more details about the plate (pattern completion), and realize it is an anniversary gift from last month, by extracting this information from episodic memory (wherein the fear/anxiety response may be re-activated). Any number of these processes can be influenced pharmacologically, and in this manner the effects of anesthetics on memory can be sorted out [82, 83]. A useful conceptualization (taxonomy) of information flow processing is that proposed by Tulving, the serial-parallel-independent model of memory [43, 57]. This is just one of a number of conceptualizations of memory. but is helpful to know as it incorporates a holistic conceptualization from sensation to long term memory. Anesthetic effects on memory, particularly as regards to unconscious learning during anesthesia, can be thought of in these terms. Some other hierarchical conceptualizations are referenced [84–86].

Serial Parallel Independent (SPI) Model of Memory

The acronym "SPI" is meant to indicate that the interaction among the three major components of this model is dependent on the memory process in play at the time (Fig. 3.6). The three components are arranged in a hierarchical fashion, with input from the outside world coming into the perceptual representation system (PRS). During encoding, information is processed in a Serial fashion, passing from PRS to semantic memory, which collates and decodes sensory input with

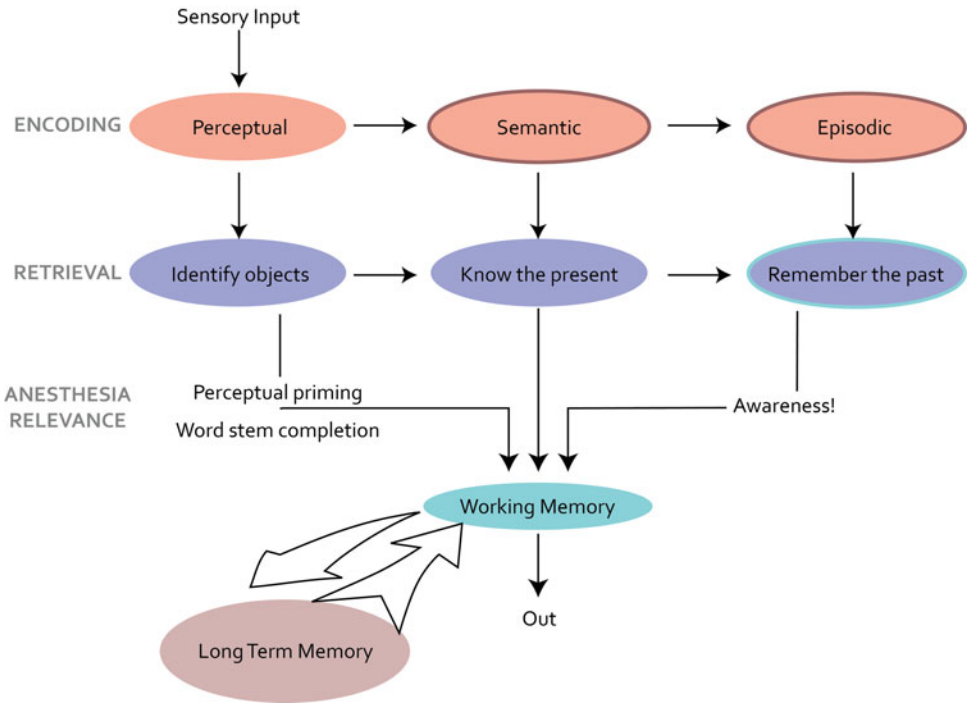

Fig. 3.6 The SPI memory system of Tulving. SPI stands for serial parallel independent model. Three large memory systems representing the perceptual representation system (PRS), semantic, and episodic memory are related in a hierarchical fashion during encoding, where information processing is Serial. Storage of memories is Parallel in each system, and these can be retrieved independently from other systems. Of interest during anesthesia is the PRS, the lowest "rung" of the memory processing, relating to sensory input and perception. If any memory function operates during anesthesia, it would be the PRS. It is likely that perceptual memories, if formed, would be stored in secondary sensory association cortices. On the other hand, if high level episodic memories are present during anesthesia, then "awareness" has occurred, an undesirable event if not expected by either the practitioner or patient

previous knowledge of the world (semantic memory, memory of "facts") to know what just happened. If input is similar to previous experience, it can be processed further incorporating this information (e.g., a red round object may be a ball). Novel qualities of the input are further processed in the higher level of episodic memory, where the experience can be incorporated as a novel event personally relevant in a distinct place and time (episodic memory, such as what we had for dinner last night). Episodic memory contains previous knowledge (I had steak at my favorite restaurant) with novel experiences (this event happened last night at 7 p.m. with a well-known friend). Linking of previous knowledge with novel information is mediated by the hippocampus, notably the spatial and temporal aspects of memory (where I had dinner and when I had dinner) [87]. These qualities are the hallmarks of a conscious (episodic) memory. At each level of processing, distinct forms of memory can be stored in Parallel, with perceptual representations (color, intensity, orientation, etc.) stored in the PRS, factual knowledge (red rubber ball) stored in the semantic system, and personally relevant and novel memories (I threw the red rubber ball against a wall this weekend) in the episodic memory system. A different interaction of this system is defined during recognition, where memories can be retrieved independently from each system. So red rubber ball is an independent memory of a ball, which could as easily be a blue soft ball. Importantly for understanding the interaction of anesthesia with memory is the fact that memories can be stored in the perceptual system, and then subsequently retrieved independently of the (conscious) semantic and episodic memory systems using techniques such as perceptual priming. The latter is an enhanced reaction (shorter reaction time, greater probability of choosing a previously experienced stimulus over a novel one, etc.) to a stimulus based on its perceptual representation [88].

The beauty of the SPI classification is its simplicity and power to explain diverse phenomena. For example, on the basis of being serial, input into episodic memory is dependent only on input from semantic memory, the memory of facts. However, there is no a priori requirement that these "facts" are indeed "true." Thus, if for whatever reason one has learned the fact that there are Martians who live in Area 51 of New Mexico, then one could have a conscious memory experience of meeting one at dinner last night, and that episodic memory would be as vivid and valid as another person's memory of dining with his wife. Thus, this model is useful to conceptualize how false memories arise and behave [57].

Recognition Memory: Not So Simple—Familiarity and Recollection with a Detour into Déjà vu

Recognition memory is a much more complex process than a binary decision of whether one has experienced a stimulus before. The processes of how someone recognizes that an event or stimulus has been experienced before are still very much being worked out. All authorities agree that there are different qualities present in recognition, and the reader can relate to this as we have all experienced the so-called butcher-on-a-bus phenomenon (a.k.a. "the face is familiar, but I can't remember the name"). We know we have seen someone before (they, the butcher, are familiar), but we don't remember other details from the episode such as what the person wore, their name, when we saw them, where they were, etc. These qualities are differentiated in the descriptive labels of familiarity and recollection (Fig. 3.7). The ability to remember specific details associated with the familiar face would be to recollect the memory [90, 91].

A tongue twister and key fact to remember is that recollection is not the same as recognition, but recollection is a type of recognition. How best to mechanistically explain recollection is an area of great controversy between two main hypotheses [15]. As this level of detail is now becoming relevant to actions of anesthesia on memory, it is now topical for anesthesiologists to understand these issues.

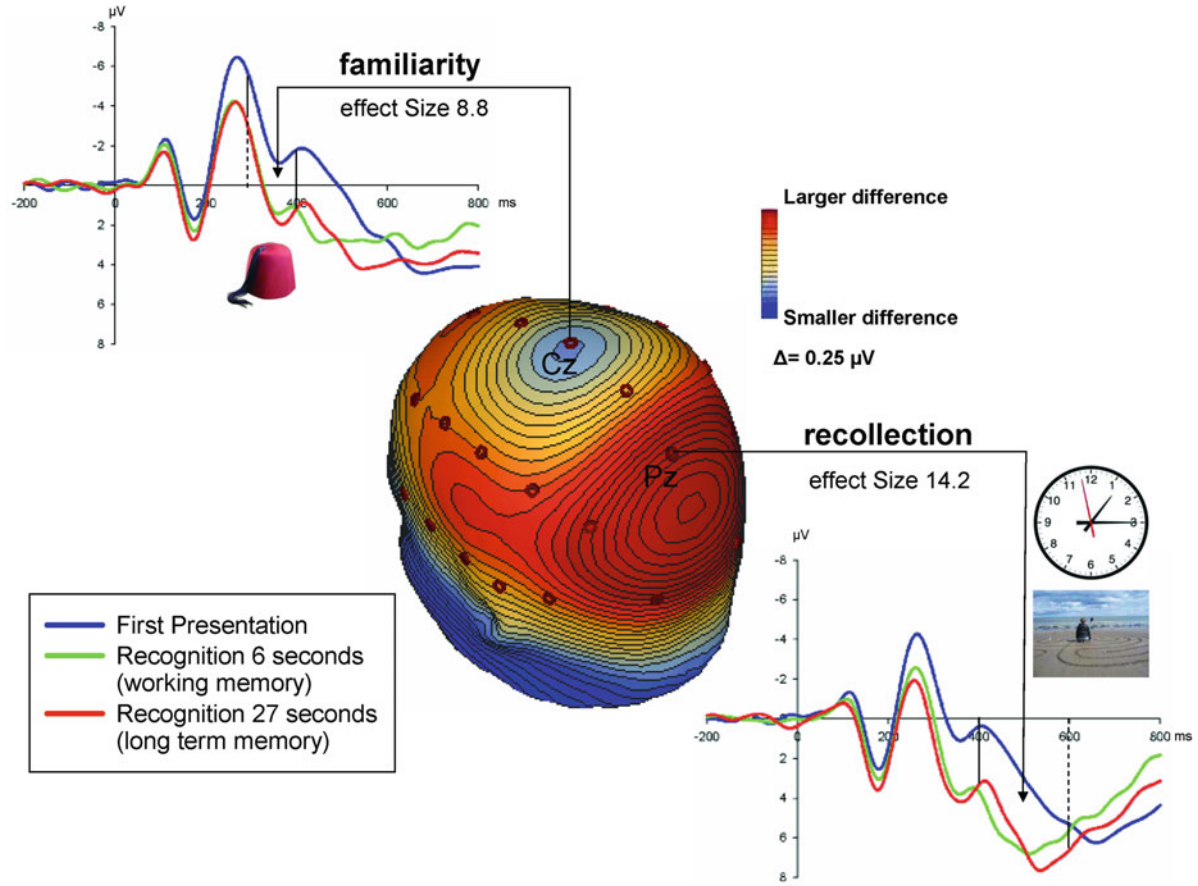

Fig. 3.7 Recognition of a conscious memory produces two different qualities we have all experienced, a fast "familiarity" reaction (I've seen this before, the "fez" is familiar) and a more elaborate recollection reaction of an event located in a time and space in our memories (a day at the beach, for example). Objective measures of brain activity recorded during these intertwined processes can be obtained using the electroencephalogram (EEG). Electrical activity of the brain can be averaged to cancel out "random noise" (EEG activity not related to the recognition task) to reveal the Event-Related Potentials (ERP) of memory processes. The ERP of a memory of a stimulus (*red* and *green wavy lines*, versus a new stimulus, *blue wavy line*) is larger in amplitude than a novel stimulus. The familiarity component of recognition occurs earlier than recollection, and is located in a somewhat different brain region (central Cz electrode versus parietal Pz electrode) [Reproduced from Veselis RA, et al. Propofol and midazolam inhibit conscious memory processes very soon after encoding: an event-related potential study of familiarity and recollection in volunteers. Anesthesiology. 2009;110(2):295–312 [89]. With permission from Wolters Kluwer Health, Inc.]

A recent study has shown that previous experience of general anesthesia in young children seems to affect one type of recognition memory, namely recollection, but not the familiarity qualities of recognition [92, 93]. The axiom of "as long as the study is reasonably well done, the attendant observations are rarely disputed" applies to this study. This is one of the few carefully done studies of memory and anesthesia in children. In this study, children who had anesthesia were carefully matched with controls, and both were tested (in the absence of any anesthetic drug) for the recollection and familiarity aspects of recognition memory. Although overall recognition was similar in both groups, a measurable difference in recollection was observed. The question of neurotoxicity of anesthetics, especially in children, is a looming problem, so this concrete observation is most noteworthy [94]. Controversy arises about how best to explain these observations. The authors of the study interpreted their findings using the "dual process" theory of memory. However, one should be aware of other explanations, and be open to different interpretations down the road. To better understand the underpinnings of this study, I will detail how one would study familiarity versus recollection recognition memory.

Differences between familiarity and recollection are studied using study-test paradigms as previously described. The added ingredient to tease out the type of recognition is a measure of confidence (or bias) of the recognition. Thus, during the recognition task, after an item is either recognized as previously seen (old) or not (new), a measure of confidence is obtained [95]. This measure varies among studies, but the most common one is to use a 6 point scale, from "absolutely sure old" (with "moderately sure old,, "somewhat sure old" in between) to "absolutely sure new" (or "somewhat sure new," "moderately sure new"). Similar information can be obtained in animal models by ingenious manipulations of reward strategies, where choice of reward is biased by previously learned preferences [47, 48]. A receiver operator characteristic (ROC) curve is plotted of these responses. In this type of analysis the ROC is the cumulative recognition proportion against false alarms rate (a false alarm is an item that is recognized as old, but is in fact a new item) across the six levels of confidence. So, for example, the left most point is the (old) recognition of highest confidence. Thus, the person is virtually certain they got the right answer, and typically about 20 % of old items are correctly recognized as being old (the *y* axis), and very few truly new items are incorrectly recognized with high confidence as being old (false alarms, thus, close to 0 % plotted on the *x*-axis) (Fig. 3.8). Then the next least confidence category is added cumulatively to the previous score, thus the next point is always greater in both axes. As a consequence these graphs generally have 5 unique points (as the last cumulative value is always 100 %). A curve interpolation graphically describes recognition performance. A set of recognitions that are largely or solely based on familiarity will produce an ROC curve that is characteristically symmetrical along the 45° axis. On the other hand, recognitions based on recollection produce an offset at "sure old" category (at the lowest false alarm rate), and tend to produce a linear response as confidence decreases. Further information can be gained by statistically normalizing scores across a Gaussian distribution (z-scores, which produce a z-ROC). In the case of z-ROC's familiarity recognitions produce a flat line, as the distribution of signal strengths is Gaussian in nature, whereas an inverted curve is present for recollection, which has a non-Gaussian or skewed distribution. Measures of familiarity and recollection as embodied in ROC curves are robustly observed. Controversy rages over what mechanisms produce these observed behaviors.

Mechanisms to explain how these curves may be generated falls into two main camps, the so-called dual process theory and single process/signal strength theory [96, 97]. There seem to be more publications that interpret observations as dual process theories (as was done in the paper describing memory impairments in children receiving anesthesia), so I will present this first. Dual process theories basically state that mechanisms supporting recollection are different from those that support familiarity. Part of this difference is related to the neuroanatomical underpinnings of these processes, with the hippocampus primarily involved in recollection (whereas single process "theorists" posit that the hippocampus is involved in both recollection and familiarity recognitions) [98, 99]. Dual process theorists provide substantial evidence that familiarity based recognition seems to be centered on other medial temporal lobe structures, in particular the parahippocampal regions [100–105]. Familiarity is the easiest to understand conceptually, and is characterized by Gaussian signal strength distributions with recognition occurring when the separation in signal peaks (between different items) is large enough. These processes are thought to be very efficient in their implementation, and occur almost automatically. In fact, this can be measured using electrophysiologic methods such as event-related potentials [89, 104, 106–108]. The onset of familiarity processes occur some 100 ms sooner than recollection processes (Fig. 3.7). Details of how these mechanisms may be instantiated neurobiologically will be presented below. If there is low signal strength or signal peaks are close together (old and new items are very similar to each other), then the confidence in familiarity is low, and the behavioral correlate would be "unsure new/old" i.e., the 3rd or 4th confidence categories. However, if the signal strength is high or signals are well separated, then one might state "sure new" or "sure old." It is important to keep in mind that signal strengths are modeled by Gaussian distribution curves. On the other hand, a recollection

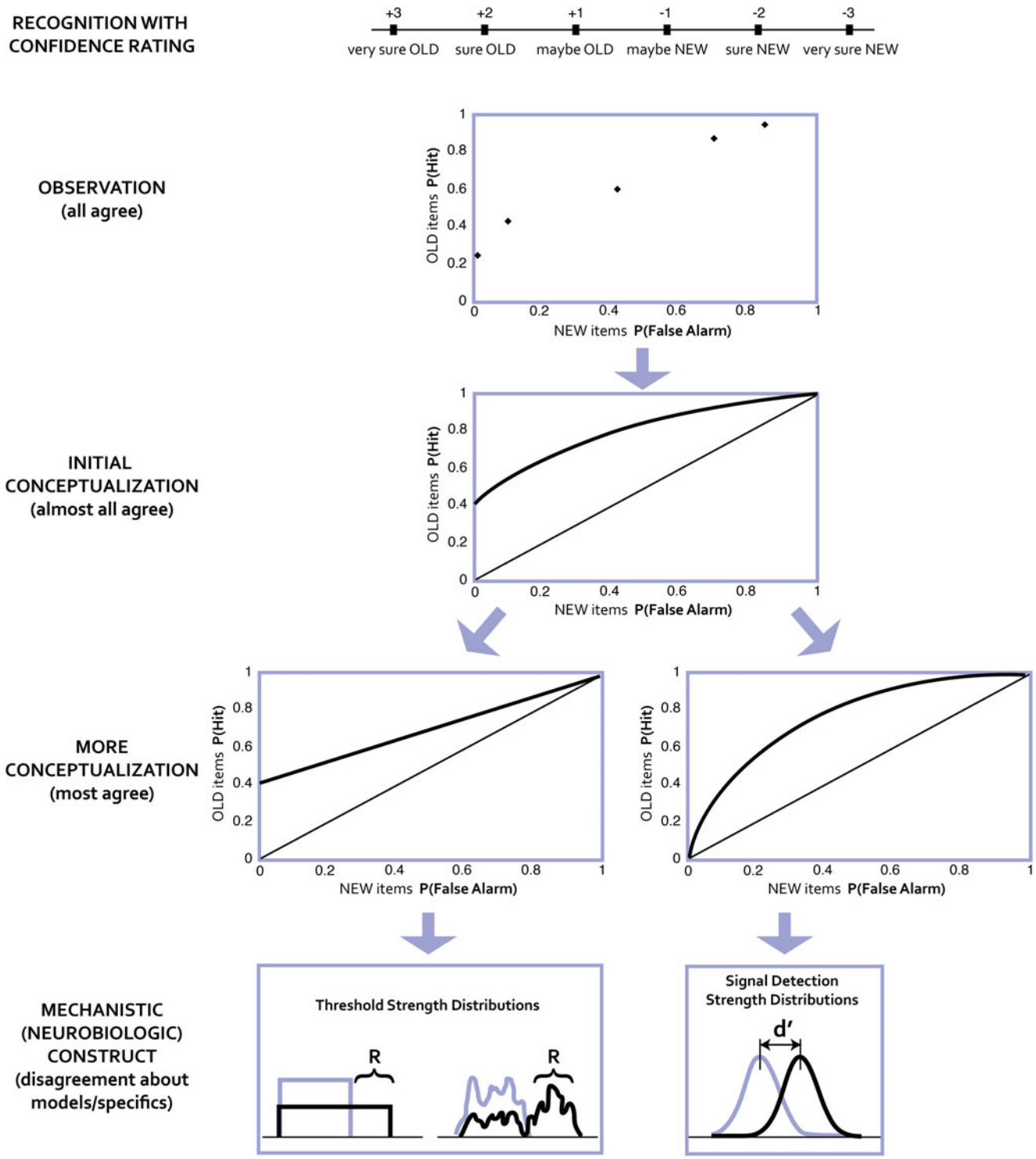

Fig. 3.8 A method to measure the contribution of familiarity versus recollection in recognition memory. This is also an illustrative example of the difficulty in translating observations, which are generally agreed upon, into a conceptualization, which may have a number of alternatives to explain the observations. A receiver operator characteristic curve is created by assessing the confidence of the recognition memory from a surety that the stimulus is old (previously experienced) to surety that it was never experienced (new). See text for details. The methodology to create the ROC curve is fairly standard and widely used. The curve represents the combined contributions of familiarity and recollection to recognition memory. How these contributions are conceptualized is important in understanding memory systems, with two alternative explanations, the dual process versus single process theory, holding sway in different camps. Both conceptualizations use different explanations of why the ROC curve looks the way it does, and why it changes appearance when certain parameters are changed in study paradigms. The dual process theory postulates that familiarity and recollection are separable processes, where familiarity is a process that depends on separation of signals between two Gaussian distributions to separate new and old events, whereas a more complex recognition process is present for recollection. In the latter case, the hippocampus acts as a pattern detector where a certain threshold criterion needs to be met before recognition can occur. The single process theory postulates a single memory process that behaves differently under differing circumstances based on the strength of memories

recognition involves not only the primary stimulus (e.g., the person's face), but also associated details (the party, the clothes, the date). In mechanistic terms one can model this as pattern completion, and when a certain number of details are matched, then recollection of the full pattern occurs. The additional processing required to test pattern matches explains why recollection processes start later and take longer than familiarity processes. On the flip side, if insufficient pattern completion is present then no recollection may occur, i.e. a memory failure. A Gaussian distribution of signal strength will always yield some degree of recognition, be it ever so small. Thus, in the dual process theory recollection is posited as a threshold process (note that the threshold effect applies to the recollection, not the recognition which can also include familiarity processes). Below this threshold no recollection occurs, and any recognition that occurs would be solely based on familiarity. If one is above this pattern completion threshold, then recognition is primarily based on recollection. Recollection would be expected to typically produce a "sure old" response, and the threshold effect is used to explain the offset of the ROC curve at the "sure old" response. Thus two processes (familiarity and recollection, dual processes) are used for recognition. In fact, everyone agrees on the latter statement, however it is emphasized again that the specifics of how these processes come into play in producing a recognition response are thought to be different in dual process versus single process models.

In the single process model theorists posit that both familiarity and recollection processes are continuous expressions of signal strength, but that recollection embodies additional details about the memory. In most experimental paradigms, these additional details are tested by measuring source memory. Thus, instead of just presenting "word" during the study phase, "word" is presented in different locations on the computer screen, with a different color from other words in different locations in the stimulus list. When recognition of word is tested for, the participant is also asked where on the screen or what color the word was. Retrieval of these additional details provides evidence of recollection rather than familiarity (and this was the paradigm used in the study comparing children who had or did not have general anesthesia) [92, 93]. Dual process theories predict that an old recollection response will not occur until a certain number of these details are present, whereas single source theories state that source memory is integral to the memory itself, no matter what strength that memory is.

Needless to say, arguments on either side have not been compelling enough to abate the controversy. The important point the reader has to appreciate is that one needs to be extremely careful not to conflate reliable observations with postulated mechanisms that produce these observations. Thus the findings of Stratmann et al. robustly show some degree of memory impairment in children who have undergone general anesthesia, which affects recollection out of proportion to familiarity [92]. However, one should be very hesitant to postulate some neurotoxic effect on the hippocampus as a result of anesthesia, be it ever so appealing, until a great deal of additional corroborating evidence is available.

Now, let us take a little detour into the experience of déjà vu to illustrate again the importance of maintaining a divide between observation and explanation. This is a memory feeling we have all likely experienced at one time or another (at least about 80 % of people do). It is the feeling of having experienced a current ongoing event sometime before, with the memory being of excruciating clarity (internally one might think "I know I have experienced these exact events before, I can almost know what will happen next") [109]. There is no accepted explanation for this memory feeling, but a most interesting one is that there is a timing problem between different memory systems, namely working and long term memory. This produces a feeling of experiencing the exact same events (which in fact have only happened once) at different times. Normally information flows in an orderly fashion through working memory (the "here and now") into long term memory (something that happened at some time in the past). However, if long term memory mechanisms somehow simultaneously have access to the contents of working memory, one could experience the same event as happening now and simultaneously in the past [110]. On the other hand, others explain déjà vu as an instantiation of familiarity, or error in pattern completion by the hippocampus [111, 112]. These examples illustrate that there is general agreement on the observations of déjà vu, in no small part due to the fact many of us have personally experienced this. However, when it comes down to explanation of these events, no one knows what particular conceptualization explains these phenomena. It is generally agreed that the neurobiologic mechanisms producing déjà vu are incorporated in the medial temporal lobes, as these feelings can be induced by electrical stimulation of these regions in epileptic patients [112]. Whether the same would occur in normal subjects is unknown, these people would never have electrodes implanted. It may be that the same end result, déjà vu, can arise via different mechanisms, everyone may be correct!

Under the Hood: The Neurobiologic/ Neurocomputational Instantiation of Conscious Memory Processes

The report of HM, who was the key index case in the series of cases reported by Scoville and Milner, began the era of understanding memory processes in terms of

neuroanatomical, and subsequently neurobiologic and neurocomputational systems (the terms "in vitro," "in vivo" now include "in computo") [113]. In brief, the famous report of Scoville described a severe impairment in the ability to form new episodic memories (e.g., memorizing a word list) after bilateral removal of a substantial amount of material from the medial temporal lobes. The material contained not only the hippocampi, but many other medial temporal lobe structures, thus it was not until some decades later that the hippocampus was clearly identified as the seat of conscious memory. A combination of animal and patient lesion studies, where neurologic damage was more localized to the hippocampus proper led the way to this insight [38, 114]. During this period, HM had become the most studied neurologic case in history, and really solidified the concept that conscious and unconscious memory are embodied in different processes and neuroanatomy [115]. HM was able to learn unconscious memories as easily as others, e.g. the motor skill of mirror drawing, but had no recollection of any of these experiments immediately after testing. However, over the last few decades it has become equally clear that even though the hippocampus is necessary for conscious memory, it is not sufficient. A complex web of interactions with other brain regions is needed for conscious memory function. As information flow progresses from sensation to long term memory, more and more interactions are needed, and wider and wider regions of brain areas function coherently in networks to support memory function [116, 117].

Interactions between different brain regions occur in the language of oscillations which provide a rich grammar for communication, ranging from frequencies to coherence, to phase shifts [118, 119]. Of particular note is that oscillations in the gamma and theta ranges seem to be very important in memory processes (as well as consciousness, and anesthetic effects thereon) [29, 120–127]. The divisions of the EEG frequency band (i.e., alpha, beta, theta, gamma, etc.) are arbitrary and based on historic interpretations of raw signals in roughly the order of discovery or description [128]. Limits between bands are also arbitrary, and change through time and with the model (human, animal) being studied [113, 129]. Theta ranges approximately from 4 to 7 Hz, whereas gamma frequencies occur at approximately 40–80 Hz. As with many processes, it is not the actual value, but changes in the value itself that are important. Thus, small changes in theta frequency, phase shift, power, etc. can be very significant. As is becoming increasing evident, it is quite a feat to describe with this level of detail how a memory process is embodied in an associated neuroanatomy and the encompassing electrophysiologic milieu. A great deal of progress has been made as details of neuronal physiology have been pinned down, and computational power of computers has increased faithfully following Moore's law. Two memory processes in particular will be considered, those being working and episodic memory as mediated through the medial temporal lobe. The latter will be considered in terms of the qualities of recollection and familiarity. As oscillatory activity in the brain is critically dependent in inter-neuronal connections, which are heavily dependent on GABAergic mechanisms, a key target of anesthetic action on memory may be modulation of electrophysiologic interactions of neuronal networks [130–139].

Working Memory

The first differentiation of memory processes was between short and long term memories. After this insight, short term memory was conceptualized as a series of closely related working memory processes [140, 141]. Working memory is embodied largely in the pre-frontal cortex, richly connected to the medial temporal lobe [142–145]. Details of how information is held in working memory have been worked out in terms of electrophysiology. One can now explain why the capacity of working memory is 7 ± 2 items in terms of oscillatory activity [30]. Purely by using characteristics of neuronal electrophysiology, an underlying slower wave action of frequency theta (hippocampal theta rhythms) can contain information in the form of superimposed faster gamma activity. It turns out that the ratio of gamma to theta (40:4 Hz) is about 7 [146, 147] (Fig. 3.9). As you may note the ratio is closer to 10, but information is contained in only a certain portion of the theta rhythm oscillation cycle. This was one of the first neurocomputational instantiation of memory processes, and others have followed.

Episodic/Conscious Memory

The behavior of more complex systems can be embodied in computational models based on neural networks. A computational neural network structure is created out of interconnected elements, where the rules for response in each element are well defined and usually simple (e.g., when the summation of inputs into the element exceeds a certain threshold value, that element then produces an output, the degree of which can be adjusted according to a weight) [148] (Fig. 3.10). As can be appreciated, each element can be considered a very simple neuron, thus the label of neural network. Most interestingly even simple designs (e.g., two-layer feed-forward network) can learn and reproduce very complex behavior. A set of data, containing input data and output results, is used to train the network to reproduce the behavior sought. Training in this context is a recurrent algorithm wherein the error term between the

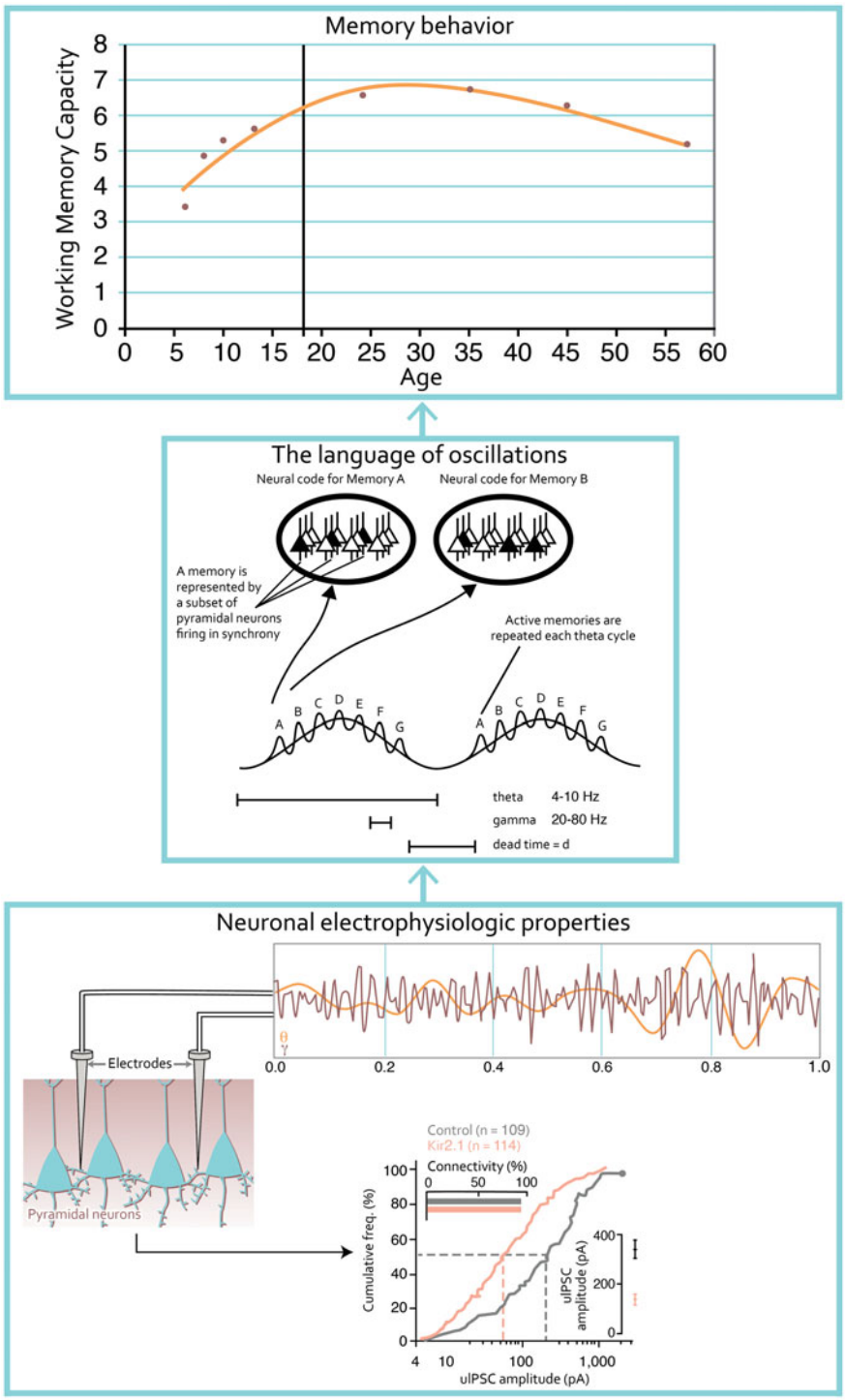

Fig. 3.9 Instantiation of working memory—from electrophysiology to behavior. The brain communicates with itself in the language of oscillations. The electrophysiologic properties of neurons as well as the architecture of their connections determine the frequency of oscillatory activity. Information is contained not only in the frequency of oscillations, but other properties such as phase relationships as well. This is an example of how one can explain why working memory can contain a maximum number of items based on representation of oscillations with differing frequencies (gamma, approximately 40 cycles/s contained within theta oscillations, approximately 7 cycles/s) which are produced by the electrophysiologic properties of neurons. The ratio of gamma to theta oscillations is roughly the capacity of working memory. Many other characteristics of memory can be related to theta and gamma oscillatory activity [middle panel reproduced from Jensen O, Lisman JE. Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. Trends Neurosci. 2005;28(2):67–72 [147]. With permission from Elsevier Ltd.]

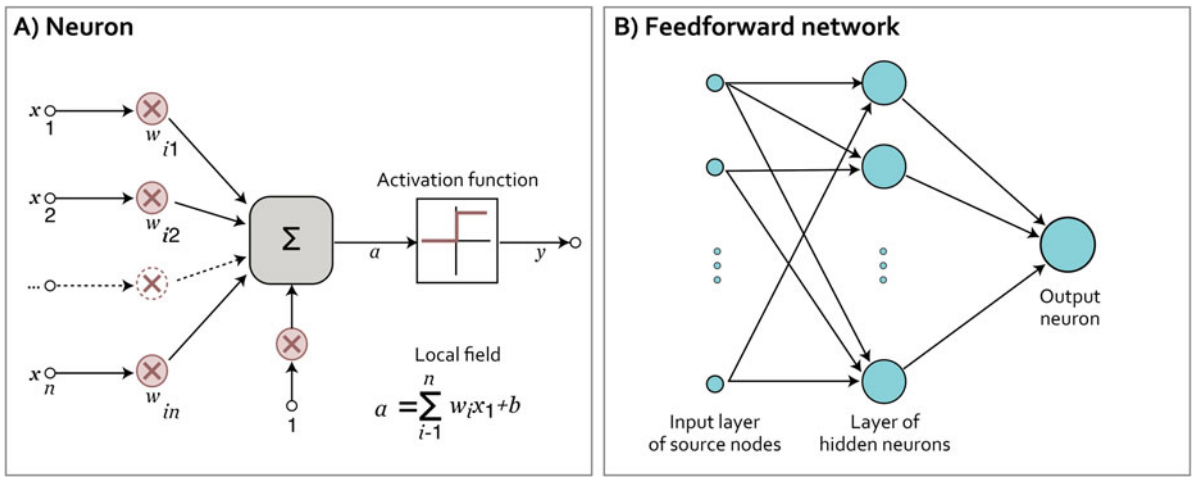

Fig. 3.10 Computational algorithms based on artificial neural networks. Artificial (computational) neural networks are loosely based on neuronal interactions with each other, but greatly simplified, to produce a learned, or trained, output from a series of inputs using Hebbian type learning. Very complex behavior can be modeled with neural networks, even when the input/output rules for each element are simple in nature. Complexity is modeled by the interactions of neural network elements ("w", i=1. . .n), and a simple two-layer feed-forward fully interconnected network is displayed. Each element processes (e.g., sums, "sigma") inputs from other elements and produces an output based on a rule (e.g., threshold activation, "activation function" in the figure). The strength of the output (inputs into the next layer) can be modified by a weighting factor. Neural networks are trained by matching a set of outputs (e.g., tidal heights) with a series of inputs (date, weather parameters, location, etc.) that are processed by a network with an initial set of weighting parameters (e.g., 0.5). An error term from the output is generated, and weights are modified iteratively to minimize this error term. When a certain acceptable error threshold is achieved, the network is then tested with a set of new (never used before) inputs and the error measured between predicted and actual outputs to assess how well the neural network models real world data. This can be done by training a network on a portion of a data set, and testing on the other part of the data set. Networks can be constructed with more elaborate configurations (e.g., recurrent inputs, more layers, pruned connections) to model even more complex behaviors

output produced by the network and the target output is minimized but adjusting the parameters governing the behavior of the network elements (primarily the weighting of the outputs for each element). For example, inputs can be the power of various EEG frequencies, and the output can be whether the EEG is of a sedated patient or an awake patient [149–152]. The trained network can be used on novel data sets to predict an output with reasonable success. As computational power and algorithms have advanced exponentially "children" of these methods are getting to the point where "the brain," as opposed to the EEG, for example, can be mathematically modeled [153, 154]. In general, there is no deterministic algorithm defined by the training process or modeling. The neural network behaves in a complex manner that is essentially a black box. Practically, neural networks work quite well in many real world situations, for example predicting tidal patterns, automated image/pattern analysis, minimal path finding, and yes, financial applications too. The use of this methodology to model neuroanatomical constructs of conscious memory will now be reviewed.

The Hippocampus

The hippocampus is a set of recurrent looping neural pathways that can very efficiently embody complex information using a sparse encoding [155–157]. The basic structure is presented in Fig. 3.11. The hippocampus is richly connected to the cortex, but the vast majority of connections are indirect. Input from the cortex is received via the entorhinal cortex, and output is through the same structure, but in a different layer (in general the cortex has six layers of neurons). Three major structures comprise the hippocampus, the dentate gyrus, and the cornu ammonis (CA) specifically the CA3 and CA1 subfields (as with many things labels are historic and somewhat poetic). A neural network model representative of hippocampal neurobiology is presented in Fig. 3.12 [158, 159]. As far as neural networks go, this is a fairly complex design. However, this is a very good model for pattern recognition. One of the first insights into the computational abilities of the hippocampus was obtained by measuring individual neuronal responses in behaving rats walking through a maze [53, 160–162]. The same sets of neurons fired when the rat was in a given location, thus the concept of place cells was discovered. The memory of a particular location is embodied in this pattern. One can think of many conscious memories (e.g., words) as a pattern. The neural network model of the hippocampus will produce a threshold type of output when a certain number of elements of a previously learned pattern are present. This is the instantiation of the recollection process, and experimental results from this computational model agree well with

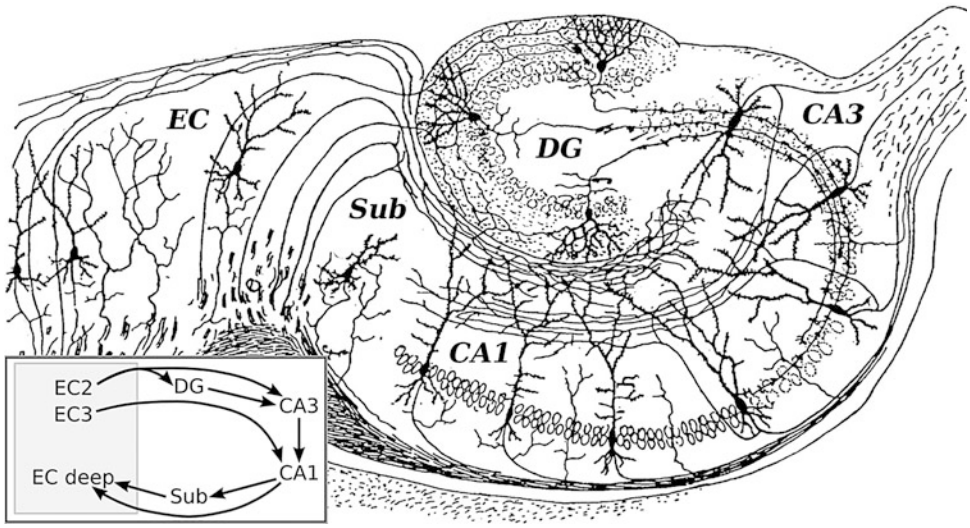

Fig. 3.11 Hippocampal architecture. This Figure is the classic histologic drawing of a rodent hippocampus Santiago Ramon y Cajal published in 1911 (Drawing of the neural circuitry of the rodent hippocampus. Histologie du Système Nerveux de l'Homme et des Vertébrés, Vols. 1 and 2. A. Maloine. Paris. 1911). Such accurate and detailed observations are still very relevant today. Included in this Figure is a conceptualization of information processing through various regions of the hippocampus. Input of information is from close-by regions in the medial temporal lobe (entorhinal cortex, EC). Sensory input via the EC projects to the dentate gyrus (DG), the CA3 and CA1 fields of the hippocampus and the subiculum (Sub) via the perforant pathway. The dentate gyrus projects to the CA3 field of the hippocampus via Mossy fibers. CA3 neurons project to the CA1 field of the hippocampus, which in turn projects back to the subiculum. The subiculum feeds back to the EC. In the EC, superficial and deep layers are arranged to produce a recurrent loop for incoming sensory information. After processing in the hippocampus, output influences information in the entorhinal reverberating circuit, which in turn repetitively activates the hippocampal formation, or is transmitted to other regions of the cerebral cortex. Thus, the hippocampus provides a very complex information processing architecture in a small amount of space, and is ideally suited in terms of pattern completion/recognition

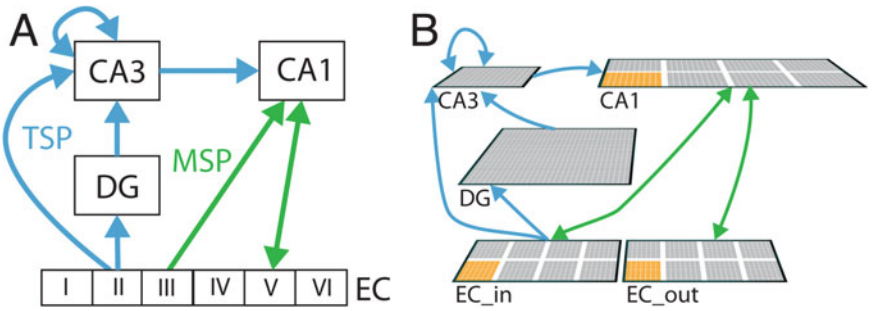

Fig. 3.12 This is a neurocomputational model of the hippocampus (a combination of Figs. 3.10 and 3.11). Most readers are familiar with the terms "in vitro" and "in vivo," and now we can add "in computo" as another way to understand details of physiologic processes. This neural network architecture can be used to understand recognition memory in humans, and can reproduce the observations of recognition memory as described in Fig. 3.8

observations [16, 76, 159]. The reader should be aware that even though this "hangs together nicely," it does not mean this is actually what happens in terms of actual physiologic processes. In a sense this is a mechanistic conceptualization. Adding to this strong circumstantial evidence is the fact that the computational model predicts certain behaviors, that, when actually tested, hold true. Further refinements in mathematical modeling are now being incorporated where, analogous to place cells, there are "time" cells [87]. One of the basic concepts of conscious memory is that an event occurs not only in a particular place, but also in a particular time. It now seems that a neurocomputational explanation can be proposed for the hippocampus to embody time as well as space.

The Rest of the Brain

A computational model of the non-hippocampally connected cortex is much simpler, where a "simple" two-layer feed-forward network can reproduce signal strength memory behavior (a.k.a. familiarity) (Fig. 3.13). As the reader is likely to appreciate, though this model of familiarity based memory works well to mimic observational results, it is

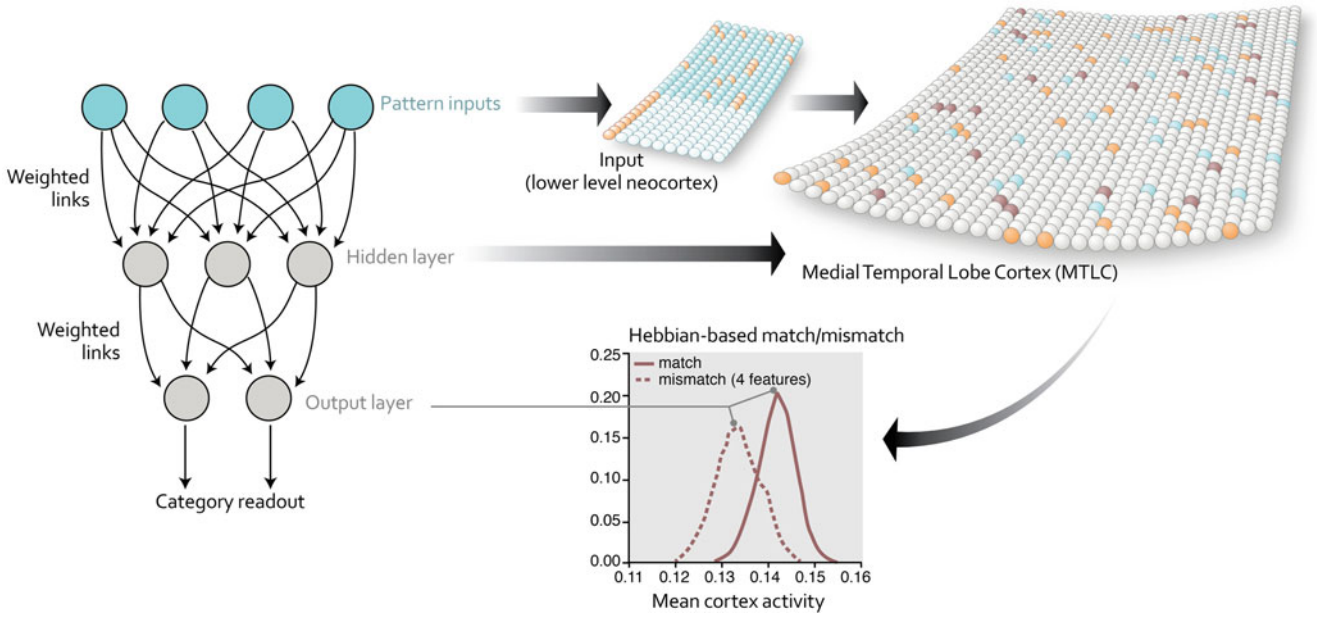

Fig. 3.13 Similar in concept to Fig. 3.12, this is a neural network instantiation of the familiarity component of recognition memory. Such "in computo" modeling can be used to investigate factors important in memory as a bridge between neurobiology and observation. Ideally the model is used to predict a certain outcome when parameters are modified in a predictable fashion. These are then tested "in vivo" to support the validity of such modeling

likely not the way the brain works. Neurons are much more complex than the elements present in a neural network model. However, this modeling is a good starting point for further research, and importantly, may serve well as a basis for investigations of anesthetic effects on memory in terms of electrophysiological mechanisms.

The "Black Box" of Unconscious Memory

To study memory requires some evidence that a memory has been created in the brain, which, as alluded to above, boils down to measuring a change in behavior. This is complex enough in the case of conscious memory, where a simple study-test paradigm can become incredibly complex by manipulation of numerous factors. The same study-test paradigm design is used to study unconscious memory, but with the added caveat that the person or animal in question has to be completely unaware that memory is being created or tested [163, 164]. This requirement is more easily attained in the case of animals, and is the reason I said that many memory behaviors in animals (e.g., object recognition) may best be compared to unconscious memory processes in humans [41]. The change in behavior indicative of the memory cannot be consciously accessible, thus all recognition paradigms mentioned above (recall, forced choice, etc.) cannot be used. To detect unconscious memory requires ingenious methods to measure such a memory. Methods include measuring some improvement in performance (e.g., faster reaction time to a previously experienced stimulus, when compared to non-experienced stimuli), or a preference for the previously (unconsciously) experienced stimulus. The latter is the basis for the previously popular subliminal advertising campaign [165]. Subliminal advertising is now highly frowned upon by society, but it could be said that if conscious perception of a product occurs in unrelated media (e.g., a movie), then "product placement" has occurred.

A large question about unconscious memory is whether it can influence future behavior. This requires two main criteria to be met, that the person is truly unaware of previous learning, and that the change in behavior is able to be replicated in a number of studies. Closely related questions include publication bias, and statistical "anomalies" where the underlying assumptions of statistical testing are not fully appreciated when conclusions are drawn, namely rejection of the null hypothesis [166, 167]. These topics are of increasing interest as clinical care is driven more and more by major studies published in reputable journals [168]. A typical study of unconscious memory might be as follows. People are asked to read stories about knowledgeable and learned scientists versus stories of sports personalities (presumably not in the running for Nobel Prizes). Then the people who have read these stories are asked to complete a general knowledge questionnaire. A study might demonstrate that people exposed to scientist stories completed the knowledge questionnaires with more correct answers. If the results of the study are positive, it is more likely to be published as being exciting new research (particularly in the psychologic

literature) [169]. To the casual reader of the literature it may appear that there is evidence of unconscious memory influence all around us, from walking faster after reading about athletes, to improved outcomes following surgery in the setting of "positive thinking." As it turns out, replication of these studies is more difficult than initially imagined. This difficulty is being appreciated more and more in studies with "hard" end points such as mortality as well. If one carefully considers the assumptions of statistical reasoning where we traditionally accept a $p < 0.05$ as being an acceptable rate of false positives, it turns out that the chance of replicating those results is somewhere around 50 % [168]. Thus, reasons for un-reproducibility may include a) the effect may not exist, and the initial positive studies were in fact false positives (estimated to be from 14 to 36 % even in well-respected peer-reviewed literature) b) there is an effect, but the current study is underpowered to replicate, or c) the study population is different in some subtle way that is difficult to ascertain (e.g., diurnal rhythms). In the case of unconscious learning, an additional problem is that not uncommonly the "unconscious" learning turns out to actually be conscious learning when the appropriate probes (e.g., de-briefing interviews of participants regarding insight) are used. Are the people really unaware that reading a story about a scientist followed by a general knowledge questionnaire has nothing to do with envy for smart people? When general interest in a particular field increases to the level that it becomes important to answer a question definitively, it is more likely that negative studies will be published, and more balanced weight of evidence will ensue. The latter is most important in the case of meta-analyses and Cochrane type reviews. The question of learning during anesthesia seems to have reached this point [170, 171]. All these factors make study of unconscious memory fascinating, while at the same time vexing. More often than not purported evidence of unconscious memory turns out to be a more complex insight into conscious memory. It is still very unclear if learning during anesthesia (if present) truly represents unconscious memory, or some degree of a weak conscious memory.

Memories are not immutable and similarly their categorizations. For example, skills and habits are considered by classical taxonomy to be unconscious memory. For example, one should try singing the national anthem starting with the third line without silently reciting the first two lines (this is a classic situation for musicians who feel compelled to "finish the phrase" when practicing). As we all know, one has had to learn the national anthem somewhere at some time. How did this conscious memory become an unconscious memory of a habit? The same process occurs in conscious memory, where an episodic event (capitals of countries) becomes general knowledge, a semantic memory without time or context (see "time and repetition" interactions Fig. 3.3). I hope I have convinced the reader that the boundaries between the taxonomies of memory, even conscious and unconscious are at best blurry [56, 88, 117]. It does seem the trend is towards a richer, more integrated appreciation of memory, without a return to the previous unitary concept of memory [172]. As an example, modeling of recollection and familiarity as separate processes using separate neural networks predicts observed behavior very well. However, if the neural network is designed to incorporate both recollection and familiarity constructs into the same network model, lo and behold, very similar results are obtained, the combined network also models observed behavior just as well [76]. As neural networks are "black boxes" to a large extent, how or why this happens remains a mystery. But this may, in fact, be the way our brains work.

Thus, currently, while we know a great deal about conscious memory, the same cannot be said of unconscious memory, particularly in regards to underlying mechanisms supporting these memory processes. Needless to say, this is one reason it is difficult to apply neurocomputational modeling to unconscious memory as has been done for conscious memory. The best conceptualization we have of unconscious memory is that of information flow [43, 56]. Unconscious memories have to be formed from information obtained from the outside world, which by necessity has to get into the brain through sensory cortices. At some point in information collation and processing, unconscious information (e.g., shape, size, intensity, color, orientation, frequency, etc. of a stimulus) becomes a conscious percept. At that point we know we just saw a red rubber ball, maybe one that we used to play with as children. Thus the best we can do with a neurobiologic instantiation of unconscious memory formation is to model information flow from the outside world before it becomes a fully conscious percept, which then has an opportunity to become a conscious memory.

The Neurobiology of Unconscious Memory

The neurobiology of unconscious memory may best be related to the lowest "rung" of the SPI model of memory, the perceptual system (note that "perceptual" is used in the psychological sense, and refers to sensation, not the percept of consciousness). Automatic processing of stimuli, one aspect of which is to filter out extraneous information whilst directing attentional resources to events of interest (orienting reflex), allows one to learn very complex information without being aware of the specifics of that information. In other words, we can learn rules that are complex without ever knowing the rules (subliminal learning) [173]. Compared with conscious memory, very little investigation has been undertaken to understand the basis of unconscious memory. But what little is known reveals a complex underpinning for this behavior. As with conscious memory, information transfer and communication between different brain regions must occur for learning to take place [88, 173]. The type of

memory learned as "unconscious" memory during anesthesia is likely different from that studied in humans in the absence of drug during unconscious rule learning. Lower processing power may be needed to form implicit, perceptual memories during anesthesia than unconscious rule learning. The neurobiologic underpinning for rule versus perceptual (sensory) learning may be quite different, though with some overlap of mechanisms likely. Thus, while there is some degree of likelihood of sensory (perceptual) memory formation during anesthesia (as detailed below), there seems to be much less likelihood of the type of learning as embodied in unconscious rule learning, as the latter requires mechanisms such as information transfer across distant brain regions which are likely to be non-functional during anesthesia.

Anesthetic Effects on Memory

Three large bodies of research exist in this field, those being (1) the effects of anesthetics on conscious memory, which include fear modulation of memory and differential effects on recollection and familiarity processes, (2) the issue of awareness, and (3) the ability to learn unconscious memory during anesthesia (Fig. 3.14). Failure of the "anesthetic system," which includes human system processes as well

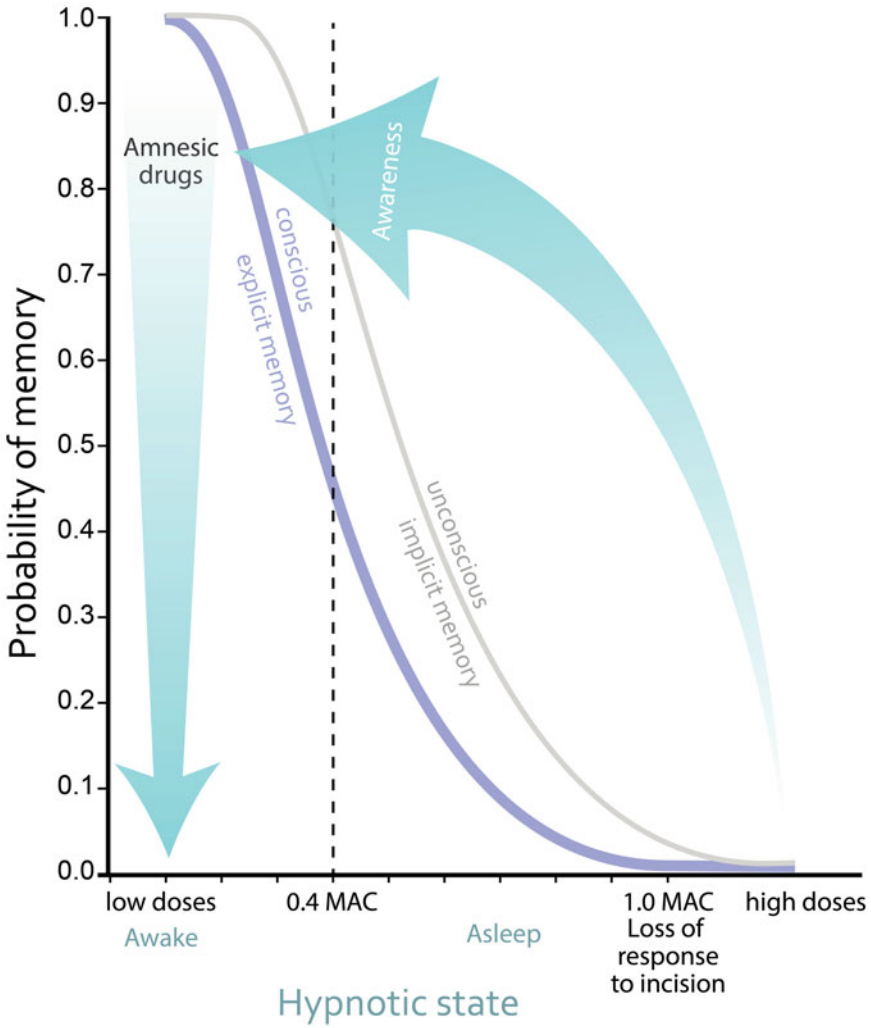

Fig. 3.14 The conceptual relationships between anesthesia and memory. The dose response curve between conscious (explicit) memory and increasing doses of anesthesia is well established, with decreasing probability of memory formation as anesthetic doses increases. When a dose of anesthetic associated with 50 % probability of movement to skin incision (one minimal alveolar concentration—MAC) is present, no chance of conscious memory formation is present. For almost all CNS depressants (most anesthetics), a dose of 0.4 MAC will produce an ~50 % probability of memory impairment on the basis of sedation (inattention to the environment). It is hypothesized that a similar dose response curve is present for unconscious memory, but is shifted to the right (more resistance to anesthesia). However, this is much less certain, as it is very difficult to quantitate unconscious memory formation. Well established is also the effect of amnesic drugs such as midazolam and propofol, which result in a low probability of conscious memory formation at low doses of drug. When one believes the patient is experiencing 1 MAC of anesthesia, but in fact less anesthetic is present (e.g., technical failure of delivery device), conscious memory is functional when the patient is not expecting this, and awareness results

as drugs, to ablate conscious memory when the patient expects no memory is covered by the somewhat vague term "awareness," again not to be confused with the concept of being aware in the sense of consciousness (though, these are closely related). A brief discussion of awareness will be undertaken only to put this huge field of investigation into context regarding memory. The majority of literature of anesthetic effects on unconscious memory relates to the question of whether learning can occur during anesthesia when conscious memory function is not present [174, 175]. Learning during anesthesia is commonly described as implicit memory formation during anesthesia. A much smaller question is the impact of anesthetic drugs on implicit (unconscious) memory during consciousness (i.e., during sedation). The difficulties of differentiating conscious from unconscious memory processes in the setting of mild sedation are formidable, and I will not review this literature, as it is at best confusing.

Anesthetic Effects on Conscious Memory: How Do We Make Patients "Not Remember a Thing!"?

When we're asleep we are disconnected from the outside world [31, 58]. Our brains are busy re-processing memories of the day's events, a portion of which we may experience in our dreams [10, 176–178]. Similarly, during anesthesia we become disconnected from processing sensory input even though sensory input is still being registered, and will be discussed in the section on learning during anesthesia. Thus, information from the outside world cannot become a conscious memory, as not enough processing power is present to form that conscious memory. An unexpected conscious memory that occurs during anesthesia falls under the category of awareness during anesthesia, discussed briefly in the next section. Normally, the practicing anesthetist prevents memory formation by putting their client to sleep. This in itself is not very interesting from a mechanistic point of view, but the transition to this state is, on the other hand, most interesting. If the dose of anesthetic agent can be held to one that produces sedation ("almost sleep"), some degree of conscious memory mechanisms are still functional, and the possibility of memory formation is present.

For sensory information to become a conscious memory (which hereafter in this section will be simply referred to as "memory"), attention must be paid to that information. There is a large body of literature examining the influence of attention on memory formation, and in practice we do use this trick to influence memory formation [179–184]. An example is engaging a patient in conversation while we start an intravenous injection. Most anesthetic agents produce memory impairment in the sedative dose range by interfering with attention (the opposite way of stating this is "producing sedation"). Sedation interferes with information processing in the early stages of memory formation, namely transfer of information from working memory to long term memory [89, 185]. As stated previously, if information disappears from working memory, it is gone forever unless it has been processed into long term memory. Thus, a person who is drunk can walk home in an impaired (sedated), but still barely functional state (for example, stopping before crossing a street with traffic in it), but will have no memory of the excursion back home. Working memory is sufficiently functional to process and react to current events, but these are not subsequently transferred to long term memory. The neurobiologic underpinnings of sedative anesthetic actions, not surprisingly, mimic those of natural sleep, and involve structures in the hypothalamus and other deep brain areas [186–189]. These same neural circuits also seem to be involved in the loss of consciousness that occurs with anesthesia. In practice, the great advantage of preventing memory formation by producing sedation is that we have a real time measure of sedative effect, such as reaction time, slurred speech, eyelid closure, responsiveness, etc. This allows critical titration of drug to desired effect (the clinical end-point of having a patient snoring). Proceeding into a state of sedation/unresponsiveness and coming out of it seems to occur along two different neural/time paths, producing a hysteresis effect [190, 191]. It may be more difficult to arouse a person from sedation once it is established. In other words, the drug concentration associated with awakening may be quite a bit less than that needed to produce unresponsiveness. Sometimes, one can observe an interesting exception to this natural history in that a person can be experiencing concentrations of anesthetic agent that normally produce deep sedation or unresponsiveness, but nevertheless can still respond to external stimuli (e.g., following simple commands) [60]. However, in this state the person may be unable to process other inputs, and be "floating" in a state of "disconnectedness," with various degrees of recall afterwards. The term "dysanesthesia" has been applied to this most interesting state of (un?)consciousness. It is still very unclear if this state is unique to anesthesia, and how best to reproduce it for further study.

As opposed to sedation, some anesthetic agents have unique effects on memory, producing amnesia for events that transpire in the presence of low concentrations of these drugs [192, 193]. Benzodiazepines are the prototypical class of drugs that produce this effect. At concentrations of drug that produce amnesia, sedation is largely absent. Thus the drunkard above becomes the slightly intoxicated person that had their gin and tonic spiked with flunitrazepam (Rohypnol), GHB (gamma hydroxybutyrate), or similar "club" drug. Persons intoxicated in such a fashion may function at a much better level, and seem to be quite awake and unimpaired. Yet, recall of events is much less likely, the amnesia is much more dense [194].

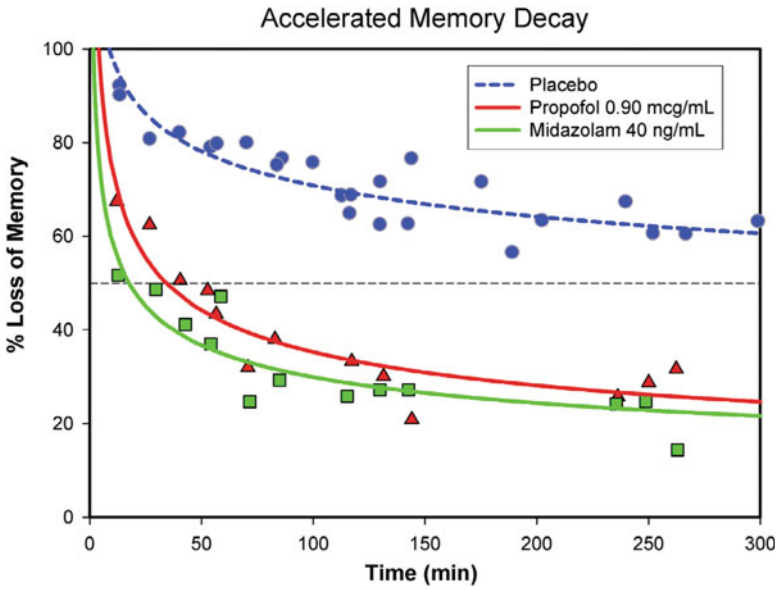

Fig. 3.15 Amnesic drug actions on conscious memory. The low probability of memory formation with amnesic drugs is apparent only after an initial period of memory decay, 15–50 min. Accelerated memory decay occurs when information is learned in the presence of midazolam or propofol. The *top blue line* represents the normal rate of forgetting of information in the placebo group. As Ebbinghaus demonstrated, memory is forgotten over time. These curves represent the loss of memories encoded into long term memory during an encoding task just before time = 0 at which point drug infusion was stopped. When midazolam or propofol were present at low concentrations during the encoding task, those items encoded into long term memory were forgotten at an accelerated rate compared with placebo. Most of the differences in forgetting from placebo happened in the first 45 min. After this time the decay curves are essentially parallel, indicating that consolidation processes that are in play after 45–90 min are not differentially affected by these drugs. The decay of memory can be modeled as a power decay function, and the parameters of this model represent memory impairment due to sedation (lambda in Fig. 3.5a, initial condition) or to lack of consolidation (psi in Fig. 3.5a, accelerated memory decay)

Careful study of memory processes in the presence of low doses of midazolam or propofol reveals the mechanism of this action to be the rapid loss of memories [72]. Details of how amnesic drugs affect memory are best understood in context of information flow from the outside world into a long lasting memory (Fig. 3.15). Terminology is a bit confusing, and one can be led astray by this. As described previously, awareness of the "here and how" occurs in working memory, a limited store of what has just come in from the outside world. Items in working memory can be remembered as long as they are continuously refreshed (rehearsal), think of memorizing a 10 digit phone number. It is easier to remember the first and last digits of the number, the serial position effect. The initial digits are likely already in long term memory, and the last digits heard are in working memory. To critically study the difference between working memory and long term memory processes a paradigm has to be used that prevents rehearsal of any items in working memory, so that one can determine if recognition of an item is truly from working or long term memory. Such a paradigm is the continuous recognition task, where items are presented every few seconds, with items repeated at short (1 or 2 intervening items) or long (10, 20 or 30 intervening items) [72, 82, 89, 195, 196]. The task of the person is to indicate if the item is new (presented the first time) or old (a repeat from the previous set of items). Importantly attention has to be paid to each item as it is presented (is it old or new?), thus preventing rehearsal of any items in working memory. As the capacity of working memory is about 7 items, and if items are presented every 3 s, then an item can reside in working memory no longer than about 20 s. If an item is correctly recognized from more than 10 items previously, then it must be remembered from "long" term memory. This is the confusing part of terminology in that "long" term memory is any time interval longer than working memory, i.e. about 20 s (not very long term in most people's minds). Using this methodology, one can determine if a drug affects working memory (lack of recognition of short interval items), or only long term memory (lack of recognition of longer interval items). Indeed, the sedation effect of drugs affects working memory, whereas amnesic drugs allow long term memories to be formed [89]. However, when these initially recognized items are tested at longer and longer intervals, 10 min, 30 min, 4 h, we find that items initially remembered from long term memory disappear very quickly (in comparison with placebo) [72]. Working and long term memory processes can be indexed by electrophysiologic measurements (event-related potentials), and reveal additional details. This explains the dense amnesia of amnesic drugs. Even if the memory is formed initially, it rapidly disappears. The fact that working memory is largely intact means that behavior in

the "here and now" is relatively normal, the person just can't remember what happened at all the night before. This type of amnesia occurs only in the presence of drug, not before, and not after the drug concentration falls to critically low levels on the basis of redistribution of metabolism. Something about the amnesic drug prevents long term memories from being consolidated into lasting memories. The specifics of what happens are still unknown.

The decay characteristics of long term memories formed in the presence of drug can be carefully measured and modeled using a power decay function, and thus the degree of amnesic versus sedative effect of a drug can be quantitated. As mentioned in the previous paragraph, the amnesic effect of a drug must act on some aspect of the sum of processes needed to consolidate a newly formed memory into one that lasts substantially longer. This inhibitory action must occur soon after memory formation, for if it acted much later, then recent memories formed at an earlier time than drug administration would also disappear. Such an effect would be characterized as retrograde amnesia, as depicted in the movies when a traumatic event has occurred. To date no study in humans has documented such a retrograde amnesic effect of any anesthetic drug [197]. In practice, we "ensure" amnesia by administering small doses of these agents, usually midazolam, before noxious events. One should be aware that by giving an amnesic drug, we cannot "erase" previously experienced memories. However, we never know how successful amnesia is until we can debrief the patient some time after the events. It could be that the dose of midazolam used was too low to produce the dense amnesia that was sought.

An interesting field of investigation is how anesthetic effects on memory translate to the pediatric patient population. It is known that working memory doesn't fully develop until quite late, about age 20 or so [198]. Another interesting fact is that most anesthetics influence memory through GABAergic mechanisms, and GABAergic receptor expression changes with age, with different effects in different cortical layers [199]. There are also some animal data that indicate long term memory effects of anesthetics (potentially a marker of neurotoxicity) can be mediated by GABA receptors [133]. Thus, much needs to be clarified regarding anesthetic effects on memory in the pediatric patient population. This will be challenging as this is a difficult age group in which to perform behavioral studies, those being the necessary condition to understand memory.

Awareness During Anesthesia: Interaction with Memory Systems

Awareness during anesthesia represents the ability of conscious memory processes to function in a situation in which they are expected not to be functional. This statement highlights the two "prongs" of this issue. One is fairly straightforward in that episodes of awareness are invariably associated with concentrations of anesthetic agents that are too low to suppress conscious memory formation and retention (consolidation) [200]. As discussed in the previous section conscious memories can be formed but then quickly forgotten in the presence of amnesic agents such as propofol or midazolam. There are ethical dilemmas that revolve around the issue of whether anesthetic practice that depends on lack of consolidation of conscious memories is considered anesthesia [201]. In practical terms this means the patient is "awake" in the presence of an amnesic drug, but has no recollection of events that happened in this state later. One issue that raises ethical concerns in some people's minds may be the duration of this amnesic state. This practice seems to be readily accepted, for example during awake intubations, or the increasingly rare "wake-up test" during neurosurgery, but is frowned upon by some for longer periods of time in a state of "dysanesthesia" where comfortable awareness may be present in a state of dissociation from external stimuli [202]. As mentioned elsewhere in this chapter, multiple states of being may be possible in the presence of anesthetics, and some of these may indeed occur only in the presence of anesthetics rather than having analogs in other situations [31, 58].

The other "prong" of awareness is expectation. It seems that if a complete explanation is provided to the patient of what is likely to happen, awareness is much less distressing, as this was what is expected. This is routinely attested to by the practice of having the patient awake and responsive during critical times during brain surgery ("awake craniotomies"), where preservation of eloquent cortex is the goal of this procedure. In fact, this procedure was standard practice in the era of H. M.s surgery, and now has been rediscovered. as being the best monitor of which part of the brain is important for a certain function, such as language or counting. Analogous to detecting a memory, behavior is the key observation of interest. The importance of patient expectation is attested to by the fact that in situations where sedation is the goal of anesthesia, the occurrence of unexpected awareness can be every bit as distressing as that which occurs during anesthesia where complete unresponsiveness is the goal [203]. Too commonly, patients undergoing sedation for procedures are told by someone that they "won't remember a thing" (which is usually true). This may help reduce anxiety before the procedure, but may also be a dis-service to our patients when sedation is not as deep as the patient was expecting.

Awareness is closely linked with the emotional memory system, mediated through the amygdala. One might consider post-traumatic stress disorder as a "wind-up" phenomenon of the fear mediated memory system. A significant incidence of PTSD can occur with awareness, and it is somewhat

unclear how to best capture these events [204–206]. It appears that PTSD can occur at a time quite distant from the inciting event. Routine post-op questioning reveals a very low incidence, by an order of magnitude, of awareness when comparison is made to formal studies of awareness [207, 208]. Why this is the case is unclear, but has been noted in a number of studies. The determine correctly the incidencd of PTSD in the setting of awareness requires longitudinal studies which are excruciatingly difficult and expensive to do, thus data on this are quite sparse at this time. Equally sparse are data on the effects of anesthetics on the fear mediated memory systems [82, 209]. It not only makes sense, but is also a fact that emotive stimuli require higher concentrations of anesthetic agents to prevent them from becoming memories [83]. A few studies have examined the effects of low doses of sevoflurane or propofol on amygdalar function and memory formation, and it does seem that the amygdala is more resistant to the effects of anesthetics. Whether the behavioral observations are linked to the neuroanatomical findings is still an open question.

The goal of reducing "awareness" to zero incidence will require changes in anesthetic practice to eliminate errors in administration (e.g., disconnected IV during TIVA) as well as ensuring appropriate patient expectations. The former can be largely addressed by "being aware of awareness" (e.g., use of checklists, protocolized hand-offs with change in personnel, etc.), and the latter by improving the informed consent process [210, 211].

Learning During Anesthesia, Is It Possible? What Is the Evidence?

The decade of the 1950s was an era of intense stresses with the possibility of global destruction just a button push away. We were surrounded by evidence of this reality from Bikini atoll to Sputnik. The Cold War exploded into full swing and there seemed to be no place to hide. Thus it is no surprise that we looked for answers to unanswerable questions anywhere we could, and one of these places was the unconscious mind. This was the era of "subliminal messages" in advertising [165]. If we could not stop the Manchurian candidate, then why not try to gain some monetary advantage? One wonders if it was just a co-incidence that the first interest in what our minds were doing during anesthesia was born in this cultural context. The first investigations into this issue were quite dramatic, exemplified by statements such as "When questioned at a verbal level he may have no memory at all for the material covered in this [surgical] interval . . . The next step is to ask permission of the subconscious to release this deeply remembered material." [212]. Thus, under the right circumstances, using specialized hypnotic techniques, one could peer into the dark unconscious where seemingly every occurrence during the anesthetic experience was faithfully recorded [213]. These concepts fit in quite well with efforts to manipulate the subconscious mind to good and not so good ends. It is no wonder that we continue to this day to desperately seek the truth about what happens in our minds during anesthesia. Despite the multitude of studies that find no evidence of any ability to influence our minds during anesthesia, we hang on to the studies that seem to provide hope that we can influence our unconscious minds which in turn can affect our behavior (positive suggestions, etc.). Are positive results hints of the truth, or, in fact an attempt to assuage a more fundamental need in our human experience?

As the reader can appreciate by now, the evidence to support or refute the formation of memories during anesthesia is roughly equal on both sides of the equation [174, 175]. Over the decades and despite manipulations of, or control for, depth of anesthesia, analgesia, anesthetic regimen, etc. there still is no insight into why there is such variability in results [170, 214–220]. One possibility is a significant "file-drawer" effect, where negative studies are less likely to gain publication, thus it is difficult to weigh the evidence in a Cochrane type analysis [221]. Such publication bias seems to be particularly relevant for social sciences, and one can regard this field as an intersection between these and the "hard" science of mechanisms of anesthesia. One might regard hypnotic methods as a "sociologic" type of approach whereas more recent studies focus on more controlled methods [171, 213]. Just as the presence of memories can only be detected (in practical terms) by looking for changes in behavior after formation of a memory, the only way behavior can be affected by a previous event is by the formation of a memory. Thus the evidence that external events during anesthesia can affect our post-anesthetic behavior is sought in the presence of memories formed during anesthesia. The best methodology to detect unconscious memories is as yet unclear [171]. The behaviors sought must be those not under conscious control (otherwise what is detected is a conscious memory) [163, 164]. Thus, the design of a typical study is to present stimuli (almost always auditory in nature) during clinically adequate anesthesia while the depth of anesthesia is being measured (e.g., using BIS), and then measure a preference for presented versus non-presented stimuli after the anesthesia has worn off. The preference is measured by "the first word that comes to mind" when presented with the first few letters of a word (word stem completion), or by measuring reaction time, for example while reading the words (or a story) [214, 222]. Evidence of unconscious memory is established by a difference in reaction to presented versus non-presented stimuli (at a certain level of statistical likelihood), and some evidence that the memory is not conscious. The latter is usually

established by negative recall or recognition tests, or by manipulation of task instructions. For example, the process dissociation procedure incorporates an additional task to "name a word that comes to mind that is *not* the first word you think of." This cognitive procedure requires a conscious manipulation of memory [223]. The results of this task are compared with those of unconsciously mediated word stem completion. There is disagreement on how best to implement the process study procedure when studying learning during anesthesia. Hazadiakos argues that a third category of memory process exists beyond conscious and unconscious, that being guessing. If one re-analyses previous studies that utilized the process dissociation procedure where unconscious memory was detected, then when the possibility of guessing is included these positive results largely disappear [171]. In a sense a more conservative statistical threshold is set by including guessing, and the underlying question is still unanswered as to what the most appropriate threshold should be [166, 167].

Even the same groups of investigators have a hard time replicating their results [219, 220]. This could be a true problem with detection of unconscious memory, or alternatively represent a statistical quandary. If one looks closely at the assumptions underlying probabilistic statistics [as opposed to predictive (e.g., Bayesian) statistics], it is clear that the probability of replication of a result in the original study is on the order of 40 %, when traditional statistical thresholds are used [166, 168]. This seems to agree very well with the historical track record of studies of learning during anesthesia. One way out of this quandary, as suggested by Avidan, is to ask the question of plausibility, is learning during anesthesia a neurobiologic possibility? [224]

There has been much progress made in understanding how anesthesia affects the brain to produce unconsciousness [225, 226]. Needless to say, the story is much more complicated than it seemed even a decade ago. These same principles likely apply to how memory processes work, being as dependent on networks and information transfer as is consciousness. Another approach to the question of learning during anesthesia is a careful consideration of a potential and plausible neurobiologic explanation of this phenomenon. If such a mechanism can be postulated, then efforts can be pursued to identify these processes, and examine anesthetic effects thereon. In short, there is sufficient evidence to support a plausible (if improbable) scenario wherein information from the outside world can be learned by the brain during anesthesia.

At this time, there is overwhelming evidence that information is sensed by the brain during anesthesia. In other words, auditory sensation (perception), though diminished, is still present during unresponsiveness [227–230]. There is really no investigation of visual sensation during anesthesia in humans. Studies focus on auditory perception, as this is the logical entry point of extraneous information of a person whose eyes are taped closed during an anesthetic (one wonders at the incidence of awareness if foam earplugs were used as routinely in the operating room) [231]. The great unknown is what happens to this sensory input after initial sensation during anesthesia? To begin to answer that question one can seek an end result (evidence of implicit memories, which, as described above, has been somewhat unfruitful), or look at processes that support further elaboration of sensory input that could eventually lead to a memory. Local connectivity seems to be intact, thus one could imagine transfer of information from primary sensory cortices to secondary association areas [232–234]. Indeed, in animals, a form of basic memory, visual object recognition memory, does ultimately reside in secondary sensory cortices [235]. This type of memory allows an animal to remember if an object has been seen before, and thus requires no further exploration when new objects are waiting to be discovered. The weight of recent literature supports the nature of this memory to be independent of hippocampal involvement, and thus would not be considered a form of conscious memory [41]. This form of memory may be similar to that sought in implicit memory studies in anesthesia. If these exist, then likely they would reside in secondary sensory cortices, the behavioral instantiation of which would be that of a sensory (perceptual) memory in the lowest rung of the SPI model of Tulving. A question to answer is how is information processed from sensory cortices to become a memory in association cortices? It seems that rather than direct transfer of information from primary to secondary (association) cortices, processing must occur through other brain structures, most likely those of the limbic system [236, 237]. If these nodes are eliminated, primitive or basic memory formation does not occur.

As much as local connectivity is present during anesthesia, connectivity between non-local (distant) regions of brain during anesthesia is severely diminished, if not absent. Feed forward information flow may be preserved, but feedback information flow is not [225, 233, 238–246]. The question that is unclear at this time is where feed forward stops during anesthesia. The critical question is whether sufficient feed-forward processing exists through other brain structures to allow transfer of information from sensory to association cortices, which can then become a perceptual (sensory) memory. Initial measures of local connectivity showed that it was preserved. Subsequently, more elegant analytic methods indicated that information content of this connectivity is low or absent [247].

Thus, one can envisage a mechanism by which memories could be formed during anesthesia, but the probability of this occurring seems quite unlikely. At the very least enough functionality of network activity must be present to allow feed-forward processing with at least some feedback to the

peri-sensory cortices. At this time very little is known about these processes, even in the absence of anesthesia, let alone during anesthesia. If indeed one could find a situation where implicit memory formation was predictable, the next issue to address is the significance of these memories. Though there is great hope that unconscious memories can influence behavior after anesthesia, at this time the best that can be hoped for is that these memories can be detected. In other research arenas, it is quite controversial whether unconscious memories have an effect on behavior. Replication studies seem to indicate that unconscious memories in fact have little influence on our behavior [164].

Conclusion

As I hope the reader appreciates by now, memory is a very complex set of phenomena, which are still being fleshed out in many directions. The field has gone from a unitary concept to that of multiple memory systems which were considered to be separate. However, as each set of processes is examined closely, they are found to interact with each other more and more closely. The neurobiologic processes supporting memory systems, also considered as separate in the past, are now being revealed as largely separate, but with many mutual interactions and similarities in basic functioning. A given neurobiologic process can be influenced to subserve different higher level systems. Thus, the hippocampus (or portions thereof) function to support some unconscious memories, and unconscious memory systems (e.g., amygdala) modulate conscious memories. Add to this mix the interaction of anesthetics, and one can imagine an almost limitless combinations of effects on memory systems ranging from subtle changes in timing of oscillatory activities in circuits to wholesale blockade of transmission of any information from one part of the brain to another. These are just beginning to be dissected out, and much cross fertilization will occur from the studies of mechanisms of the loss of consciousness from anesthetic drugs. Currently, most of our knowledge resides in the epi-phenomenal realm, i.e. how anesthetics change behavior relevant to memory. We know which drugs are amnesic, which are sedative, and those that have both properties. How these affect cognitive outcomes is just beginning to be investigated (e.g., "triple low" patients, post-operative cognitive dysfunction, delirium, neurotoxicity in children) [248–255]. If there is one thing to remember from this chapter, it is that one needs to approach the field with an open mind, and not be tethered to a particular conceptualization. An open mind in alliance with keen clinical observations will lead to new and better understandings of what we do every day.

References

1. Tulving E. Multiple memory systems and consciousness. Hum Neurobiol. 1987;6(2):67–80.
2. Tulving E, Schacter DL. Priming and human memory systems. Science. 1990;247(4940):301–6.
3. Tulving E. Memory systems and the brain. Clin Neuropharmacol. 1992;15 Suppl 1 Pt A:327A–8A.
4. Zola-Morgan SM, Squire LR. The primate hippocampal formation: evidence for a time-limited role in memory storage. Science. 1990;250(4978):288–90.
5. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science. 1991;253(5026):1380–6.
6. Zola-Morgan S, Squire LR. Neuroanatomy of memory. Annu Rev Neurosci. 1993;16:547–63.
7. Cooper SJ, Donald O. Hebb's synapse and learning rule: a history and commentary. Neurosci Biobehav Rev. 2005;28(8):851–74.
8. Hebb DO. The organization of behavior; a neuropsychological theory. New York: Wiley; 1949. p. xix, 335.
9. McGaugh JL. Memory—a century of consolidation. Science. 2000;287(5451):248–51.
10. Rudoy JD, et al. Strengthening individual memories by reactivating them during sleep. Science. 2009;326(5956):1079.
11. Gais S, et al. Sleep transforms the cerebral trace of declarative memories. Proc Natl Acad Sci. 2007;104(47):18778–83.
12. Axmacher N, Haupt S, Fernandez G, Elger CE, Fell J. The role of sleep in declarative memory consolidation: direct evidence by intracranial EEG. Cereb Cortex. 2008;18(3):500–7.
13. Hui K, Fisher CE. The ethics of molecular memory modification. J Med Ethics. 2015;41(7):515–20.
14. Hongpaisan J, Alkon DL. A structural basis for enhancement of long-term associative memory in single dendritic spines regulated by PKC. Proc Natl Acad Sci U S A. 2007;104(49):19571–6.
15. Voss JL, Paller KA. Bridging divergent neural models of recognition memory: introduction to the special issue and commentary on key issues. Hippocampus. 2010;20(11):1171–7.
16. Elfman KW, Parks CM, Yonelinas AP. Testing a neurocomputational model of recollection, familiarity, and source recognition. J Exp Psychol Learn Mem Cogn. 2008;34(4):752–68.
17. Cohen NJ, Squire LR. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. Science. 1980;210(4466):207–10.
18. Heindel WC, et al. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. J Neurosci. 1989;9(2):582–7.
19. Shallice T, Warrington EK. Independent functioning of verbal memory stores: a neuropsychological study. Q J Exp Psychol. 1970;22(2):261–73.
20. Baddeley AD, Warrington EK. Amnesia and the distinction between long- and short-term memory. J Verbal Learn Verbal Behav. 1970;9:176–89.
21. Baddeley A. The concept of episodic memory. Philos Trans R Soc Lond B Biol Sci. 2001;356(1413):1345–50.
22. Atkinson RC, Shiffrin RM. The control of short-term memory. Sci Am. 1971;225(2):82–90.
23. Melton AW. Memory. Science. 1963;140(3562):82–6.
24. Peterson LR, Peterson MJ. Short-term retention of individual verbal items. J Exp Psychol. 1959;58:193–8.
25. Brown J. Some tests of the decay theory of immediate memory. Q J Exp Psychol. 1958;10:12–21.
26. Talmi D, et al. Neuroimaging the serial position curve. A test of single-store versus dual-store models. Psychol Sci. 2005;16(9):716–23.

27. Howard MW, Kahana MJ. A distributed representation of temporal context. J Math Psychol. 2002;46:269.
28. Baddeley A. Working memory. In: Gazzaniga MS, editor. The cognitive neurosciences. Cambridge: MIT Press; 1995. p. 755–64.
29. Lisman JE, Jensen O. The theta-gamma neural code. Neuron. 2013;77(6):1002–16.
30. Lisman JE, Idiart MA. Storage of 7 +/− 2 short-term memories in oscillatory subcycles. Science. 1995;267(5203):1512–5.
31. Pandit JJ. Acceptably aware during general anaesthesia: 'dysanaesthesia'—the uncoupling of perception from sensory inputs. Conscious Cogn. 2014;27:194–212.
32. Baars BJ, Franklin S. How conscious experience and working memory interact. Trends Cogn Sci. 2003;7(4):166–72.
33. Squire LR, Knowlton B, Musen G. The structure and organization of memory. Annu Rev Psychol. 1993;44:453–95.
34. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry. 1957;20:11–21.
35. Hebb DO, Penfield W. Human behavior after extensive bilateral removal from the frontal lobes. Arch Neurol Psychiatry. 1940;44 (2):421–38.
36. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA. 2015;313(3):285–93.
37. Skirrow C, et al. Temporal lobe surgery in childhood and neuroanatomical predictors of long-term declarative memory outcome. Brain. 2014;138:80–93.
38. Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J Neurosci. 1986;6(10):2950–67.
39. Eichenbaum H. The hippocampus and mechanisms of declarative memory. Behav Brain Res. 1999;103(2):123–33.
40. Jacoby LL. Invariance in automatic influences of memory: toward a user's guide for the process-dissociation procedure. J Exp Psychol Learn Mem Cogn. 1998;24(1):3–26.
41. Winters BD, Saksida LM, Bussey TJ. Object recognition memory: neurobiological mechanisms of encoding, consolidation and retrieval. Neurosci Biobehav Rev. 2008;32(5):1055–70.
42. Smith CN, et al. When recognition memory is independent of hippocampal function. Proc Natl Acad Sci. 2014;111 (27):9935–40.
43. Tulving E. Episodic memory and common sense: how far apart? Philos Trans R Soc Lond B Biol Sci. 2001;356(1413):1505–15.
44. Gelbard-Sagiv H, et al. Internally generated reactivation of single neurons in human hippocampus during free recall. Science. 2008;322(5898):96–101.
45. Tulving E. Episodic memory: from mind to brain. Annu Rev Psychol. 2002;53:1–25.
46. Clayton NS, Dickinson A. Episodic-like memory during cache recovery by scrub jays. Nature. 1998;395(6699):272–4.
47. Fortin NJ, Wright SP, Eichenbaum H. Recollection-like memory retrieval in rats is dependent on the hippocampus. Nature. 2004;431(7005):188–91.
48. Ergorul C, Eichenbaum H. The hippocampus and memory for "what," "where," and "when". Learn Mem. 2004;11(4):397–405.
49. Shrager Y, et al. Spatial memory and the human hippocampus. Proc Natl Acad Sci U S A. 2007;104(8):2961–6.
50. Pastalkova E, et al. Storage of spatial information by the maintenance mechanism of LTP. Science. 2006;313(5790):1141–4.
51. Broadbent NJ, Squire LR, Clark RE. Spatial memory, recognition memory, and the hippocampus. Proc Natl Acad Sci U S A. 2004;101:14515–20.
52. Poucet B, Save E, Lenck-Santini PP. Sensory and memory properties of hippocampal place cells. Rev Neurosci. 2000;11 (2–3):95–111.
53. Alme CB, et al. Place cells in the hippocampus: eleven maps for eleven rooms. Proc Natl Acad Sci U S A. 2014;111:18428–35.
54. Kahana MJ, et al. Human theta oscillations exhibit task dependence during virtual maze navigation. Nature. 1999;399(6738):781–4.
55. Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev. 1992;99 (2):195–231.
56. Saksida LM. Neuroscience. Remembering outside the box. Science. 2009;325(5936):40–1.
57. Windhorst C. The slave model of autobiographical memory. Cogn Process. 2005;6(4):253–65.
58. Sanders RD, et al. Unresponsiveness not equal unconsciousness. Anesthesiology. 2012;116(4):946–59.
59. Mashour GA. Integrating the science of consciousness and anesthesia. Anesth Analg. 2006;103(4):975–82.
60. Pandit JJ. Isolated forearm—or isolated brain? Interpreting responses during anaesthesia—or 'dysanaesthesia'. Anaesthesia. 2013;68(10):995–1000.
61. Wixted JT. The psychology and neuroscience of forgetting. Annu Rev Psychol. 2004;55:235–69.
62. Parker ES, Cahill L, McGaugh JL. A case of unusual autobiographical remembering. Neurocase. 2006;12(1):35–49.
63. Lynch MA. Long-term potentiation and memory. Physiol Rev. 2004;84(1):87–136.
64. Hinrichs JV, Ghoneim MM, Mewaldt SP. Diazepam and memory: retrograde facilitation produced by interference reduction. Psychopharmacology (Berl). 1984;84(2):158–62.
65. Medved MI, Hirst W. Islands of memory: autobiographical remembering in amnestics. Memory. 2006;14(3):276–88.
66. Gilboa A. Autobiographical and episodic memory—one and the same? Evidence from prefrontal activation in neuroimaging studies. Neuropsychologia. 2004;42(10):1336–49.
67. Burianova H, Grady CL. Common and unique neural activations in autobiographical, episodic, and semantic retrieval. J Cogn Neurosci. 2007;19(9):1520–34.
68. Fischer S, et al. Motor memory consolidation in sleep shapes more effective neuronal representations. J Neurosci. 2005;25 (49):11248–55.
69. Brashers-Krug T, Shadmehr R, Bizzi E. Consolidation in human motor memory. Nature. 1996;382(6588):252–5.
70. Wixted JT. On common ground: Jost's (1897) law of forgetting and Ribot's (1881) law of retrograde amnesia. Psychol Rev. 2004;111(4):864–79.
71. Wixted JT, Carpenter SK. The Wickelgren power law and the Ebbinghaus savings function. Psychol Sci. 2007;18(2):133–4.
72. Pryor KO, et al. Visual P2-N2 complex and arousal at the time of encoding predict the time domain characteristics of amnesia for multiple intravenous anesthetic drugs in humans. Anesthesiology. 2010;113(2):313–26.
73. Kapur S, et al. Neuroanatomical correlates of encoding in episodic memory: levels of processing effect. Proc Natl Acad Sci U S A. 1994;91(6):2008–11.
74. Craik FIM, Lockhart RS. Levels of processing—framework for memory research. J Verbal Learn Verbal Behav. 1972;11 (6):671–84.
75. Dehaene S, et al. Imaging unconscious semantic priming. Nature. 1998;395(6702):597–600.
76. Elfman KW, Yonelinas AP. Recollection and familiarity exhibit dissociable similarity gradients: a test of the complementary learning systems model. J Cogn Neurosci. 2014;1–17.
77. Murray MM, Foxe JJ, Wylie GR. The brain uses single-trial multisensory memories to discriminate without awareness. Neuroimage. 2005;27(2):473–8.
78. Busse L, et al. The spread of attention across modalities and space in a multisensory object. Proc Natl Acad Sci U S A. 2005;102 (51):18751–6.
79. Shtyrov Y, Hauk O, Pulvermuller F. Distributed neuronal networks for encoding category-specific semantic information:

the mismatch negativity to action words. Eur J Neurosci. 2004;19 (4):1083–92.
80. Picton TW, et al. Mismatch negativity: different water in the same river. Audiol Neurootol. 2000;5(3–4):111–39.
81. Näätänen R. Attention and brain function. Hillsdale, NJ: L. Erlbaum; 1992. p. 494.
82. Pryor KO, et al. Effect of propofol on the medial temporal lobe emotional memory system: a functional magnetic resonance imaging study in human subjects. Br J Anaesth. 2015;115 Suppl 1: i104–13.
83. Pryor KO, et al. Enhanced visual memory effect for negative versus positive emotional content is potentiated at sub-anaesthetic concentrations of thiopental. Br J Anaesth. 2004;93(3):348–55.
84. Henson RN, Gagnepain P. Predictive, interactive multiple memory systems. Hippocampus. 2010;20(11):1315–26.
85. Shimamura AP. Hierarchical relational binding in the medial temporal lobe: the strong get stronger. Hippocampus. 2010;20 (11):1206–16.
86. Cowell RA, Bussey TJ, Saksida LM. Components of recognition memory: dissociable cognitive processes or just differences in representational complexity? Hippocampus. 2010;20 (11):1245–62.
87. Eichenbaum H. Time cells in the hippocampus: a new dimension for mapping memories. Nat Rev Neurosci. 2014;15(11):732–44.
88. Rose M, Haider H, Buchel C. The emergence of explicit memory during learning. Cereb Cortex. 2010;20(12):2787–97.
89. Veselis RA, et al. Propofol and midazolam inhibit conscious memory processes very soon after encoding: an event-related potential study of familiarity and recollection in volunteers. Anesthesiology. 2009;110(2):295–312.
90. Rugg MD, Yonelinas AP. Human recognition memory: a cognitive neuroscience perspective. Trends Cogn Sci. 2003;7(7):313–9.
91. Wais PE, Mickes L, Wixted JT. Remember/know judgments probe degrees of recollection. J Cogn Neurosci. 2008;20 (3):400–5.
92. Stratmann G, et al. Effect of general anesthesia in infancy on long-term recognition memory in humans and rats. Neuropsychopharmacology. 2014;39(10):2275–87.
93. Eichenbaum H. Remember that? Or does it just seem familiar? A sophisticated test for assessing memory in humans and animals reveals a specific cognitive impairment following general anesthesia in infancy. Neuropsychopharmacology. 2014;39(10):2273–4.
94. Hemmings HC, Jevtovic-Todorovic V. Special issue on anaesthetic neurotoxicity and neuroplasticity. Br J Anaesth. 2013;110 Suppl 1:i1–2.
95. Yonelinas AP. Receiver-operating characteristics in recognition memory: evidence for a dual-process model. J Exp Psychol Learn Mem Cogn. 1994;20(6):1341–54.
96. Yonelinas AP, et al. Signal-detection, threshold, and dual-process models of recognition memory: ROCs and conscious recollection. Conscious Cogn. 1996;5(4):418–41.
97. Wixted JT. Dual-process theory and signal-detection theory of recognition memory. Psychol Rev. 2007;114(1):152–76.
98. Sauvage MM, et al. Recognition memory: opposite effects of hippocampal damage on recollection and familiarity. Nat Neurosci. 2008;11(1):16–8.
99. Wais PE, et al. The hippocampus supports both the recollection and the familiarity components of recognition memory. Neuron. 2006;49(3):459–66.
100. Yonelinas AP, et al. Recollection and familiarity deficits in amnesia: convergence of remember-know, process dissociation, and receiver operating characteristic data. Neuropsychology. 1998;12 (3):323–39.
101. Duzel E, et al. Brain activity evidence for recognition without recollection after early hippocampal damage. Proc Natl Acad Sci U S A. 2001;98(14):8101–6.
102. Kahn I, Davachi L, Wagner AD. Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. J Neurosci. 2004;24(17):4172–80.
103. Yonelinas AP, et al. Separating the brain regions involved in recollection and familiarity in recognition memory. J Neurosci. 2005;25(11):3002–8.
104. Curran T, et al. Combined pharmacological and electrophysiological dissociation of familiarity and recollection. J Neurosci. 2006;26(7):1979–85.
105. Daselaar SM, Fleck MS, Cabeza R. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. J Neurophysiol. 2006;96(4):1902–11.
106. Curran T, Cleary AM. Using ERPs to dissociate recollection from familiarity in picture recognition. Brain Res Cogn Brain Res. 2003;15(2):191–205.
107. Opitz B, Cornell S. Contribution of familiarity and recollection to associative recognition memory: insights from event-related potentials. J Cogn Neurosci. 2006;18(9):1595–605.
108. MacKenzie G, Donaldson DI. Dissociating recollection from familiarity: electrophysiological evidence that familiarity for faces is associated with a posterior old/new effect. Neuroimage. 2007;36(2):454–63.
109. Warren-Gash C, Zeman A. Is there anything distinctive about epileptic deja vu? J Neurol Neurosurg Psychiatry. 2014;85 (2):143–7.
110. O'Connor AR, Moulin CJ. Deja vu experiences in healthy subjects are unrelated to laboratory tests of recollection and familiarity for word stimuli. Front Psychol. 2013;4:881.
111. Malecki M. Familiarity transfer as an explanation of the deja vu effect. Psychol Rep. 2015;116(3):955–82.
112. Bartolomei F, et al. Cortical stimulation study of the role of rhinal cortex in deja vu and reminiscence of memories. Neurology. 2004;63(5):858–64.
113. Fuentealba P, Steriade M. The reticular nucleus revisited: intrinsic and network properties of a thalamic pacemaker. Prog Neurobiol. 2005;75(2):125–41.
114. Rempel-Clower NL, et al. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci. 1996;16(16):5233–55.
115. Corkin S. What's new with the amnesic patient H.M.? Nat Rev Neurosci. 2002;3(2):153–60.
116. Varela F, et al. The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci. 2001;2(4):229–39.
117. Dehaene S, et al. Conscious, preconscious, and subliminal processing: a testable taxonomy. Trends Cogn Sci. 2006;10 (5):204–11.
118. Buzsaki G. Theta oscillations in the hippocampus. Neuron. 2002;33(3):325–40.
119. Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. Science. 2004;304(5679):1926–9.
120. Fell J, et al. Rhinal-hippocampal theta coherence during declarative memory formation: interaction with gamma synchronization? Eur J Neurosci. 2003;17(5):1082–8.
121. Mormann F, et al. Phase/amplitude reset and theta-gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. Hippocampus. 2005;15 (7):890–900.
122. Canolty RT, et al. High gamma power is phase-locked to theta oscillations in human neocortex. Science. 2006;313 (5793):1626–8.
123. Osipova D, et al. Theta and gamma oscillations predict encoding and retrieval of declarative memory. J Neurosci. 2006;26 (28):7523–31.
124. Nyhus E, Curran T. Functional role of gamma and theta oscillations in episodic memory. Neurosci Biobehav Rev. 2010;34(7):1023–35.

125. Lega B, et al. Slow-theta-to-gamma phase-amplitude coupling in human hippocampus supports the formation of new episodic memories. Cereb Cortex. 2014;26:268–78.
126. Roux F, Uhlhaas PJ. Working memory and neural oscillations: alpha-gamma versus theta-gamma codes for distinct WM information? Trends Cogn Sci. 2014;18(1):16–25.
127. Perouansky M, et al. Slowing of the hippocampal theta rhythm correlates with anesthetic-induced amnesia. Anesthesiology. 2010;113(6):1299–309.
128. La Vaque TJ. The history of EEG Hans Berger. J Neurother. 1999;3(2):1–9.
129. Knoblauch V, et al. Homeostatic control of slow-wave and spindle frequency activity during human sleep: effect of differential sleep pressure and brain topography. Cereb Cortex. 2002;12 (10):1092–100.
130. Baker PM, et al. Disruption of coherent oscillations in inhibitory networks with anesthetics: role of GABA(A) receptor desensitization. J Neurophysiol. 2002;88(5):2821–33.
131. Caraiscos VB, et al. Tonic inhibition in mouse hippocampal CA1 pyramidal neurons is mediated by alpha5 subunit-containing gamma-aminobutyric acid type A receptors. Proc Natl Acad Sci U S A. 2004;101(10):3662–7.
132. Cheng VY, et al. {alpha}5GABAA receptors mediate the amnestic but not sedative-hypnotic effects of the general anesthetic etomidate. J Neurosci. 2006;26(14):3713–20.
133. Saab BJ, et al. Short-term memory impairment after isoflurane in mice is prevented by the alpha5 gamma-aminobutyric acid type A receptor inverse agonist L-655,708. Anesthesiology. 2010;113 (5):1061–71.
134. Lecker I, et al. Potentiation of GABAA receptor activity by volatile anaesthetics is reduced by α5GABAA receptor-preferring inverse agonists. Br J Anaesth. 2013;110 Suppl 1:i73–81.
135. Banks MI, White JA, Pearce RA. Interactions between distinct GABA(A) circuits in hippocampus. Neuron. 2000;25(2):449–57.
136. White JA, et al. Networks of interneurons with fast and slow gamma-aminobutyric acid type A (GABAA) kinetics provide substrate for mixed gamma-theta rhythm. Proc Natl Acad Sci U S A. 2000;97(14):8128–33.
137. Benkwitz C, Banks MI, Pearce RA. Influence of GABAA receptor gamma2 splice variants on receptor kinetics and isoflurane modulation. Anesthesiology. 2004;101(4):924–36.
138. Verbny YI, Merriam EB, Banks MI. Modulation of gamma-aminobutyric acid type A receptor-mediated spontaneous inhibitory postsynaptic currents in auditory cortex by midazolam and isoflurane. Anesthesiology. 2005;102(5):962–9.
139. Burlingame RH, et al. Subhypnotic doses of isoflurane impair auditory discrimination in rats. Anesthesiology. 2007;106(4):754–62.
140. Baddeley AD. Working memory. Science. 1992;255:556–9.
141. Baddeley A. The fractionation of working memory. Proc Natl Acad Sci U S A. 1996;93(24):13468–72.
142. Blumenfeld RS, Ranganath C. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci. 2006;26(3):916–25.
143. Ranganath C, Cohen MX, Brozinsky CJ. Working memory maintenance contributes to long-term memory formation: neural and behavioral evidence. J Cogn Neurosci. 2005;17(7):994–1010.
144. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci. 2003;3(4):255–74.
145. Muller NG, Machado L, Knight RT. Contributions of subregions of the prefrontal cortex to working memory: evidence from brain lesions in humans. J Cogn Neurosci. 2002;14(5):673–86.
146. Ward LM. Synchronous neural oscillations and cognitive processes. Trends Cogn Sci. 2003;7(12):553–9.
147. Jensen O, Lisman JE. Hippocampal sequence-encoding driven by a cortical multi-item working memory buffer. Trends Neurosci. 2005;28(2):67–72.
148. Chakrabarti BK, Basu A. Neural network modeling. Prog Brain Res. 2008;168:155–68.
149. Veselis RA, Reinsel R, Wronski M. Analytical methods to differentiate similar electroencephalographic spectra: neural network and discriminant analysis. J Clin Monit. 1993;9(4):257–67.
150. Veselis RA, et al. Use of neural network analysis to classify electroencephalographic patterns against depth of midazolam sedation in intensive care unit patients. J Clin Monit. 1991;7(3):259–67.
151. Kloppel B. Application of neural networks for EEG analysis. Considerations and first results. Neuropsychobiology. 1994;29 (1):39–46.
152. Kloppel B. Neural networks as a new method for EEG analysis. A basic introduction. Neuropsychobiology. 1994;29(1):33–8.
153. Kasabov NK. NeuCube: a spiking neural network architecture for mapping, learning and understanding of spatio-temporal brain data. Neural Netw. 2014;52:62–76.
154. Gulyas A, et al. Navigable networks as Nash equilibria of navigation games. Nat Commun. 2015;6:7651.
155. Duvernoy HM, Bourgouin P. The human hippocampus: functional anatomy, vascularization and serial sections with MRI. 2nd completely rev. and expanded ed. Berlin and New York: Springer; 1998. p. viii, 213.
156. Lisman JE. Hippocampus, II: memory connections. Am J Psychiatry. 2005;162(2):239.
157. Wixted JT, et al. Sparse and distributed coding of episodic memory in neurons of the human hippocampus. Proc Natl Acad Sci U S A. 2014;111(26):9621–6.
158. Rolls ET. A computational theory of episodic memory formation in the hippocampus. Behav Brain Res. 2010;215(2):180–96.
159. Elfman KW, Aly M, Yonelinas AP. Neurocomputational account of memory and perception: thresholded and graded signals in the hippocampus. Hippocampus. 2014;24(12):1672–86.
160. O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. 1971;34(1):171–5.
161. O'Keefe J. Hippocampus, theta, and spatial memory. Curr Opin Neurobiol. 1993;3(6):917–24.
162. Samsonovich AV, Ascoli GA. A simple neural network model of the hippocampus suggesting its pathfinding role in episodic memory retrieval. Learn Mem. 2005;12:193–208.
163. Shanks DR, et al. Priming intelligent behavior: an elusive phenomenon. PLoS One. 2013;8(4), e56515.
164. Newell BR, Shanks DR. Unconscious influences on decision making: a critical review. Behav Brain Sci. 2014;37(1):1–19.
165. Bullock A. The secret sales pitch: an overview of subliminal advertising. San Jose, CA: Norwich Publishers; 2004. 272 p.
166. Ioannidis JP. Why most published research findings are false. PLoS Med. 2005;2(8), e124.
167. Johnson VE. Revised standards for statistical evidence. Proc Natl Acad Sci U S A. 2013;110(48):19313–7.
168. Avidan MS, Wildes TS. Power of negative thinking. Br J Anaesth. 2015;114(1):3–5.
169. Yong E. Replication studies: bad copy. Nature. 2012;485 (7398):298–300.
170. Lequeux P-Y, Hecquet F, Bredas P. Does anesthetic regimen influence implicit memory during general anesthesia? Anesth Analg. 2014;119(5):1174–9. doi:10.1213/ANE.0000000000000162.
171. Hadzidiakos D, et al. Analysis of memory formation during general anesthesia (propofol/remifentanil) for elective surgery using the process-dissociation procedure. Anesthesiology. 2009;111 (2):293–301.
172. Nadel L, Hardt O. Update on memory systems and processes. Neuropsychopharmacology. 2011;36(1):251–73.
173. Berns GS, Cohen JD, Mintun MA. Brain regions responsive to novelty in the absence of awareness. Science. 1997;276 (5316):1272–5.

174. Andrade J. Learning during anaesthesia: a review. Br J Psychol. 1995;86(Pt 4):479–506.
175. Ghoneim MM, Block RI. Learning and memory during general anesthesia. Anesthesiology. 1997;87(2):387–410.
176. Genzel L, et al. Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? Trends Neurosci. 2014;37(1):10–9.
177. Marshall L, Born J. The contribution of sleep to hippocampus-dependent memory consolidation. Trends Cogn Sci. 2007;11 (10):442–50.
178. Gais S, Born J. Declarative memory consolidation: mechanisms acting during human sleep. Learn Mem. 2004;11(6):679–85.
179. Uncapher MR, Rugg MD. Effects of divided attention on fMRI correlates of memory encoding. J Cogn Neurosci. 2005;17 (12):1923–35.
180. Naveh-Benjamin M, Guez J, Marom M. The effects of divided attention at encoding on item and associative memory. Mem Cognit. 2003;31(7):1021–35.
181. Iidaka T, et al. The effect of divided attention on encoding and retrieval in episodic memory revealed by positron emission tomography. J Cogn Neurosci. 2000;12(2):267–80.
182. Anderson ND, et al. The effects of divided attention on encoding- and retrieval-related brain activity: a PET study of younger and older adults. J Cogn Neurosci. 2000;12(5):775–92.
183. Coull JT. Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. Prog Neurobiol. 1998;55(4):343–61.
184. Gardiner JM, Parkin AJ. Attention and recollective experience in recognition memory. Mem Cognit. 1990;18(6):579–83.
185. Veselis RA, et al. Information loss over time defines the memory defect of propofol: a comparative response with thiopental and dexmedetomidine. Anesthesiology. 2004;101(4):831–41.
186. Nelson LE, et al. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology. 2003;98 (2):428–36.
187. Nelson LE, et al. The sedative component of anesthesia is mediated by GABA(A) receptors in an endogenous sleep pathway. Nat Neurosci. 2002;5(10):979–84.
188. Gelegen C, et al. Staying awake—a genetic region that hinders α2 adrenergic receptor agonist-induced sleep. Eur J Neurosci. 2014;40:2311–9.
189. Franks NP. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. Nat Rev Neurosci. 2008;9 (5):370–86.
190. Friedman EB, et al. A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: evidence for neural inertia. PLoS One. 2010;5(7), e11903.
191. Kelz MB, et al. An essential role for orexins in emergence from general anesthesia. Proc Natl Acad Sci U S A. 2008;105 (4):1309–14.
192. Veselis RA, et al. The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. Anesthesiology. 1997;87(4):749–64.
193. Ghoneim MM, Hinrichs JV. Drugs, memory and sedation: specificity of effects. Anesthesiology. 1997;87(Oct):734–6.
194. Schwartz RH, Milteer R, LeBeau MA. Drug-facilitated sexual assault ('date rape'). South Med J. 2000;93(6):558–61.
195. Kim M, Kim J, Kwon JS. The effect of immediate and delayed word repetition on event-related potential in a continuous recognition task. Brain Res Cogn Brain Res. 2001;11(3):387–96.
196. Friedman D. ERPs during continuous recognition memory for words. Biol Psychol. 1990;30:61–87.
197. Ghoneim MM, Block RI. Immediate peri-operative memory. Acta Anaesthesiol Scand. 2007;51(8):1054–61.
198. Fandakova Y, et al. Age differences in short-term memory binding are related to working memory performance across the lifespan. Psychol Aging. 2014;29(1):140–9.
199. Datta D, Arion D, Lewis DA. Developmental expression patterns of GABAA receptor subunits in layer 3 and 5 pyramidal cells of monkey prefrontal cortex. Cereb Cortex. 2015;25(8):2295–305.
200. Mashour GA, Avidan MS. Intraoperative awareness: controversies and non-controversies. Br J Anaesth. 2015;115 Suppl 1:i20–6.
201. Glannon W. Anaesthesia, amnesia and harm. J Med Ethics. 2014;40:651–7.
202. Pandit JJ, Russell IF, Wang M. Interpretations of responses using the isolated forearm technique in general anaesthesia: a debate. Br J Anaesth. 2015;115 Suppl 1:i32–45.
203. Kent CD, et al. Psychological impact of unexpected explicit recall of events occurring during surgery performed under sedation, regional anaesthesia, and general anaesthesia: data from the Anesthesia Awareness Registry. Br J Anaesth. 2013;110(3):381–7.
204. Whitlock EL, et al. Psychological sequelae of surgery in a prospective cohort of patients from three intraoperative awareness prevention trials. Anesth Analg. 2015;120(1):87–95.
205. Samuelsson P, Brudin L, Sandin RH. Late psychological symptoms after awareness among consecutively included surgical patients. Anesthesiology. 2007;106(1):26–32.
206. Sandin R. Outcome after awareness with explicit recall. Acta Anaesthesiol Belg. 2006;57(4):429–32.
207. Pollard RJ, et al. Intraoperative awareness in a regional medical system: a review of 3 years' data. Anesthesiology. 2007;106 (2):269–74.
208. Cook TM, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: patient experiences, human factors, sedation, consent, and medicolegal issues. Br J Anaesth. 2014;113(4):560–74.
209. Alkire MT, Nathan SV, McReynolds JR. Memory enhancing effect of low-dose sevoflurane does not occur in basolateral amygdala-lesioned rats. Anesthesiology. 2005;103(6):1167–73.
210. Starmer AJ, et al. Changes in medical errors after implementation of a handoff program. N Engl J Med. 2014;371(19):1803–12.
211. Colligan L, Brick D, Patterson ES. Changes in medical errors with a handoff program. N Engl J Med. 2015;372(5):490–1.
212. Cheek DB. Unconscious perception of meaningful sounds during surgical anesthesia as revealed under hypnosis. Am J Clin Hypn. 1959;1(3):101–13.
213. Levinson BW. States of awareness during anaesthesia: preliminary communication. Br J Anaesth. 1965;37(7):544–6.
214. Lubke GH, et al. Dependence of explicit and implicit memory on hypnotic state in trauma patients. Anesthesiology. 1999;90 (3):670–80.
215. Lubke GH, et al. Memory formation during general anesthesia for emergency cesarean sections. Anesthesiology. 2000;92 (4):1029–34.
216. Kerssens C, et al. Memory function during propofol and alfentanil anesthesia: predictive value of individual differences. Anesthesiology. 2002;97(2):382–9.
217. Kerssens C, Gaither JR, Sebel PS. Preserved memory function during bispectral index-guided anesthesia with sevoflurane for major orthopedic surgery. Anesthesiology. 2009;111(3):518–24. doi:10.1097/ALN.0b013e3181b05f0b.
218. Kerssens C, Ouchi T, Sebel PS. No evidence of memory function during anesthesia with propofol or isoflurane with close control of hypnotic state. Anesthesiology. 2005;102(1):57–62.
219. Deeprose C, et al. Unconscious learning during surgery with propofol anaesthesia. Br J Anaesth. 2004;92(2):171–7.
220. Deeprose C, et al. Unconscious auditory priming during surgery with propofol and nitrous oxide anaesthesia: a replication. Br J Anaesth. 2005;94(1):57–62.

221. Franco A, Malhotra N, Simonovits G. Social science. Publication bias in the social sciences: unlocking the file drawer. Science. 2014;345(6203):1502–5.
222. Munte S, et al. Increased reading speed for stories presented during general anesthesia. Anesthesiology. 1999;90(3):662–9.
223. Jacoby LL. A process dissociation framework: separating automatic from intentional uses of memory. J Mem Lang. 1991;33 (1):1–18.
224. Veselis RA. Memory formation during anaesthesia: plausibility of a neurophysiological basis. Br J Anaesth. 2015;115 Suppl 1:i13–9.
225. Mashour GA, Alkire MT. Consciousness, anesthesia, and the thalamocortical system. Anesthesiology. 2013;118(1):13–5. doi:10.1097/ALN.0b013e318277a9c6.
226. Mashour GA. Dreaming during anesthesia and sedation. Anesth Analg. 2011;112(5):1008–10.
227. DiFrancesco MW, et al. BOLD fMRI in infants under sedation: Comparing the impact of pentobarbital and propofol on auditory and language activation. J Magn Reson Imaging. 2013;38 (5):1184–95.
228. Plourde G, et al. Attenuation of the 40-hertz auditory steady state response by propofol involves the cortical and subcortical generators. Anesthesiology. 2008;108(2):233–42.
229. Veselis R, et al. Auditory rCBF covariation with word rate during drug-induced sedation and unresponsiveness: a H2015 PET study. Brain Cogn. 2004;54(2):142–4.
230. Heinke W, et al. Sequential effects of propofol on functional brain activation induced by auditory language processing: an event-related functional magnetic resonance imaging study. Br J Anaesth. 2004;92(5):641–50.
231. Gonano C, et al. Effect of earplugs on propofol requirement and awareness with recall during spinal anesthesia. Minerva Anestesiol. 2010;76(7):504–8.
232. Liu X, et al. Differential effects of deep sedation with propofol on the specific and nonspecific thalamocortical systems: a functional magnetic resonance imaging study. Anesthesiology. 2013;118 (1):59–69. doi:10.1097/ALN.0b013e318277a801.
233. Hudetz AG. General anesthesia and human brain connectivity. Brain Connect. 2012;2(6):291–302.
234. Boveroux P, et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology. 2010;113(5):1038–53.
235. Lopez-Aranda MF, et al. Role of layer 6 of V2 visual cortex in object-recognition memory. Science. 2009;325(5936):87–9.
236. Chen X, et al. Encoding and retrieval of artificial visuoauditory memory traces in the auditory cortex requires the entorhinal cortex. J Neurosci. 2013;33(24):9963–74.
237. Baker R, et al. Altered activity in the central medial thalamus precedes changes in the neocortex during transitions into both sleep and propofol anesthesia. J Neurosci. 2014;34(40):13326–35.
238. John ER, Prichep LS. The anesthetic cascade: a theory of how anesthesia suppresses consciousness. Anesthesiology. 2005;102 (2):447–71.
239. John ER, et al. Invariant reversible qEEG effects of anesthetics. Conscious Cogn. 2001;10(2):165–83.
240. Liu X, et al. Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory. Hum Brain Mapp. 2012;33(10):2487–98.
241. Hudetz AG, Pearce R. Suppressing the mind: anesthetic modulation of memory and consciousness. Contemporary clinical neuroscience. Totowa, NJ: Humana; 2010. p. x, 252.
242. Hudetz AG, Vizuete JA, Imas OA. Desflurane selectively suppresses long-latency cortical neuronal response to flash in the rat. Anesthesiology. 2009;111(2):231–9. doi:10.1097/ALN.0b013e3181ab671e.
243. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. Science. 2008;322(5903):876–80.
244. Imas OA, et al. Isoflurane disrupts anterio-posterior phase synchronization of flash-induced field potentials in the rat. Neurosci Lett. 2006;402(3):216–21.
245. Blain-Moraes S, et al. Neurophysiological correlates of sevoflurane-induced unconsciousness. Anesthesiology. 2014;122:307–16.
246. Lee U, et al. Dissociable network properties of anesthetic state transitions. Anesthesiology. 2011;114(4):872–81.
247. Monti MM, et al. Dynamic change of global and local information processing in propofol-induced loss and recovery of consciousness. PLoS Comput Biol. 2013;9(10), e1003271.
248. Sessler DI, et al. Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. Anesthesiology. 2012;116(6):1195–203.
249. Myles PS. Untangling the triple low: causal inference in anesthesia research. Anesthesiology. 2014;121(1):1–3.
250. Kertai MD, White WD, Gan TJ. Cumulative duration of "triple low" state of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia is not associated with increased mortality. Anesthesiology. 2014;121(1):18–28.
251. Monk TG, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008;108(1):18–30.
252. Rappaport BA, et al. Anesthetic neurotoxicity—clinical implications of animal models. N Engl J Med. 2015;372(9):796–7.
253. Riker RR, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489–99.
254. MacLaren R, et al. A randomized, double-blind pilot study of dexmedetomidine versus midazolam for intensive care unit sedation: patient recall of their experiences and short-term psychological outcomes. J Intensive Care Med. 2015;30(3):167–75.
255. Hudetz JA, et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2009;23(5):651–7.