Chapter 9
Storage and Evolution of Memes in the Brain

Contents

9.1 Storage of Memes as Memory

We have seen that genes have achieved immortality by developing perpetually replicating bodies. Through the algorithm of Darwinian evolution, bodies better suited for reproduction prevailed. A result of this evolution was the development of the brain.

Bigger brains mean more capacity for learning and memory. If you remember what was successful in your trial and error in a given situation, then you do not have to repeat the cumbersome and often dangerous trial and error to know what to do when a similar situation arises.

We discussed in the previous chapter that memory is the precursor and foundation of memes, i.e., memes are portable memory, and interconnected, assembled memories are memeplexes called ideas. Then, how is memory formed and stored in the brain?

The exact mechanism of the formation and storage of memory at the neuronal level has been elucidated recently through the works of Eric Kandel and others (Kandel, 2006) and will be discussed below.

Memory may be classified as implicit or explicit, and short term or long term. Implicit or procedural memory is the more fundamental form of memory, which is not necessarily conscious and does not necessarily involve language. It occurs in all animals. Explicit or declarative memory is subject to conscious recall and consists

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of personal experiences (episodic memory) and what we call knowledge (semantic memory), e.g., what is your name, what is the capital of the United States. Both types of memory may be short or long term.

9.1.1 Implicit Memory

9.1.1.1 Short-Term Memory

Kandel showed that learning takes place even at the level of a single synapse in the sea slug, *Aplysia californica* (Kandel, 2001). Both habituation and sensitization occur at the level of the single synapse to repeated stimuli. In the synapse between a sensory neuron and a motor neuron, habituation causes the sensory neuron to release less and less amounts of the neurotransmitter, glutamate. In sensitization, it releases more glutamate.

In sensitization, Kandel et al. discovered that serotonin-releasing interneurons play a role, modulating the synaptic strength. The interneurons have synapses both at the cell body and the presynaptic terminal of the sensory neuron. When serotonin is released at the synaptic cleft, it enters a receptor and activates cyclic AMP, which in turn activates protein kinase A. Protein kinase A then enhances the release of glutamate.

9.1.1.2 Long-Term Memory

In long-term memory, there is, in addition to enhanced release of neurotransmitter, anatomical change in the presynaptic neuron, i.e., it grows more terminals and forms more synaptic connections. The mechanism of long-term memory formation involves genetic engineering.

Kandel and colleagues showed that genes encoding for protein synthesis at the synapse were turned on in *Aplysia* when new synaptic connections were made (Kandel, 2006).

Repeated stimuli activate serotonin release by interneurons which, in turn, activates cyclic AMP in the sensory neuron which, in turn, activates protein kinase A, which moves into the nucleus together with MAP kinase which it recruited (see Fig. 9.1). In the nucleus, the kinases activate a gene regulatory protein, CREB, which binds to a promoter gene. There are two forms of CREB protein, CREB-1 and CREB-2. CREB-1 activates gene expression and CREB-2 suppresses gene expression. Protein kinase A activates CREB-1 and MAP kinase inactivates CREB-2, thus, jointly, they enhance gene expression, making proteins for the new synaptic structure. The opposing action of CREB-1 and CREB-2 in enhancing and suppressing gene expression may serve to regulate long-term memory formation, i.e., which event will be stored and which will not.

When genes are activated by CREB proteins, they produce messenger RNAs (mRNAs) that are distributed throughout the cell (see Figs. 9.2 and 9.3). The mRNAs that reach synapses are in a dormant form and do not make proteins. When

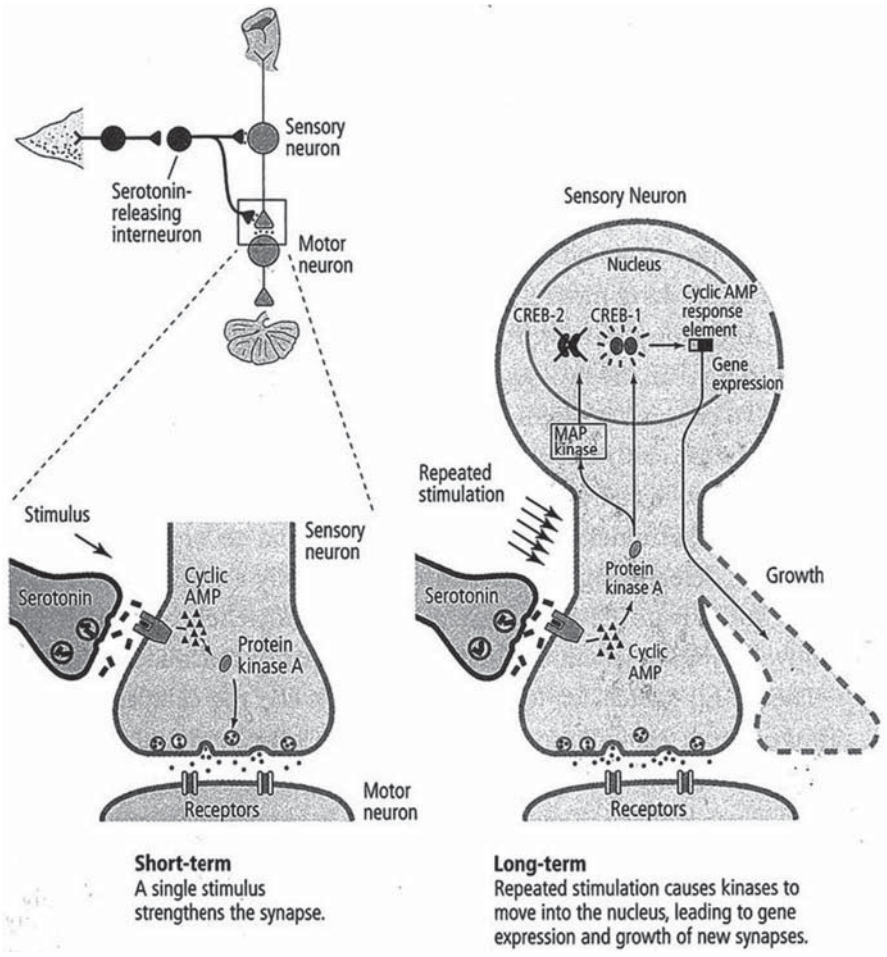

Fig. 9.1 Molecular mechanisms of short- and long-term memory. (From Kandel, 2006, p. 261, reprinted with permission)

a synapse has been repeatedly stimulated by serotonin released by an interneuron, the CPEB (cytoplasmic polyadenylation element-binding protein) that was present becomes activated, which in turn awakens the dormant mRNA, which now makes proteins and stabilizes the synapse. CPEB is a *prion-like* protein. Prions are proteins that cause the "mad cow" disease (bovine spongioform encephalopathy) and Creutzfeldt–Jakob disease. Prions can fold into two distinct shapes, an infectious (dominant) and a noninfectious (recessive) form. The noninfectious form is a normal protein found throughout the body. The infectious form is self-perpetuating and can transform the noninfectious form into the infectious form. There are normal genes that encode prions giving rise to the noninfectious form, but it can become infectious by contact with infectious prions, or sometimes spontaneously. Thus prion infection

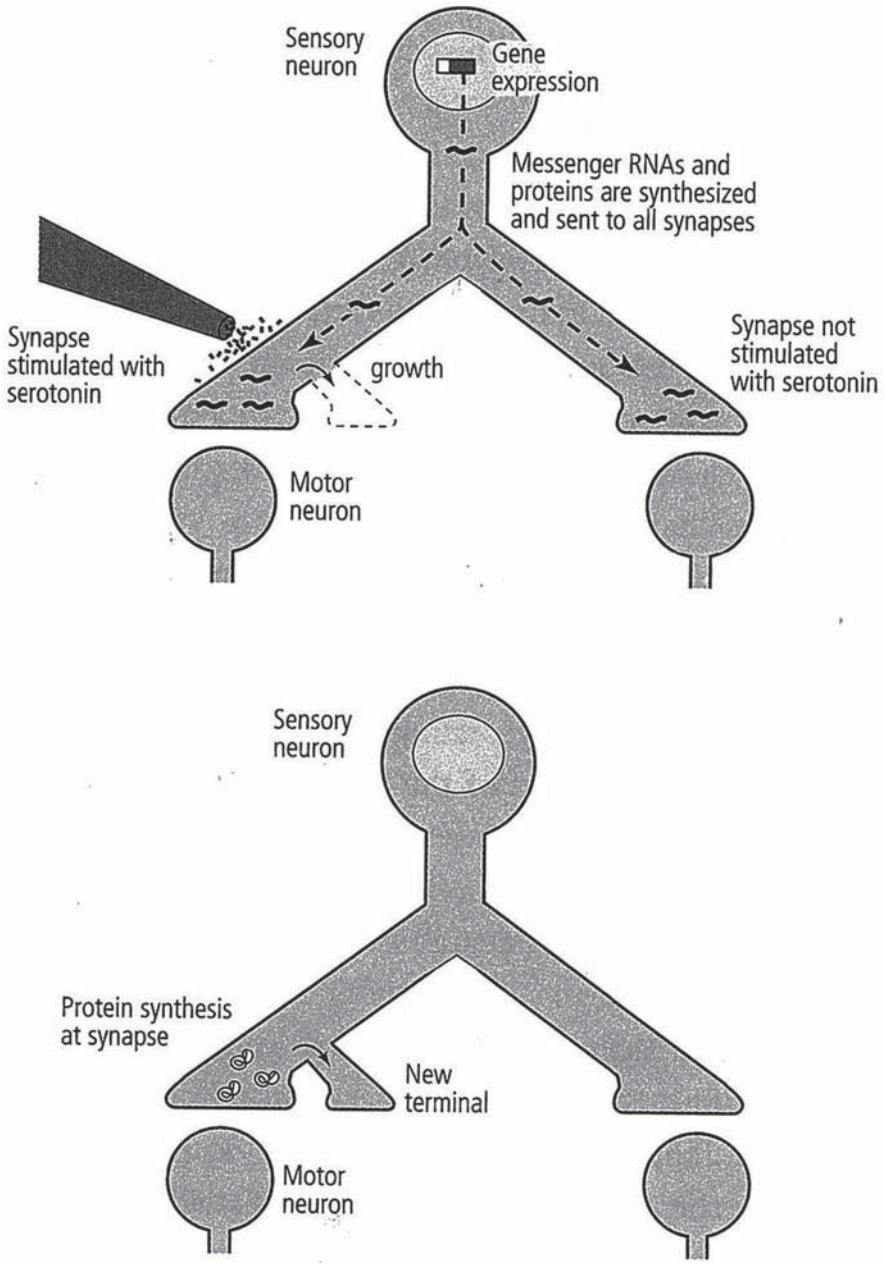

Fig. 9.2 Two mechanisms of long-term change. New proteins are sent to all of the synapses (*above*). Only synapses stimulated with serotonin use them to initiate the growth of new terminals. Proteins synthesized locally (*below*) are needed to sustain the growth initiated by gene expression. (From Kandel, 2006, p. 271, reprinted with permission)

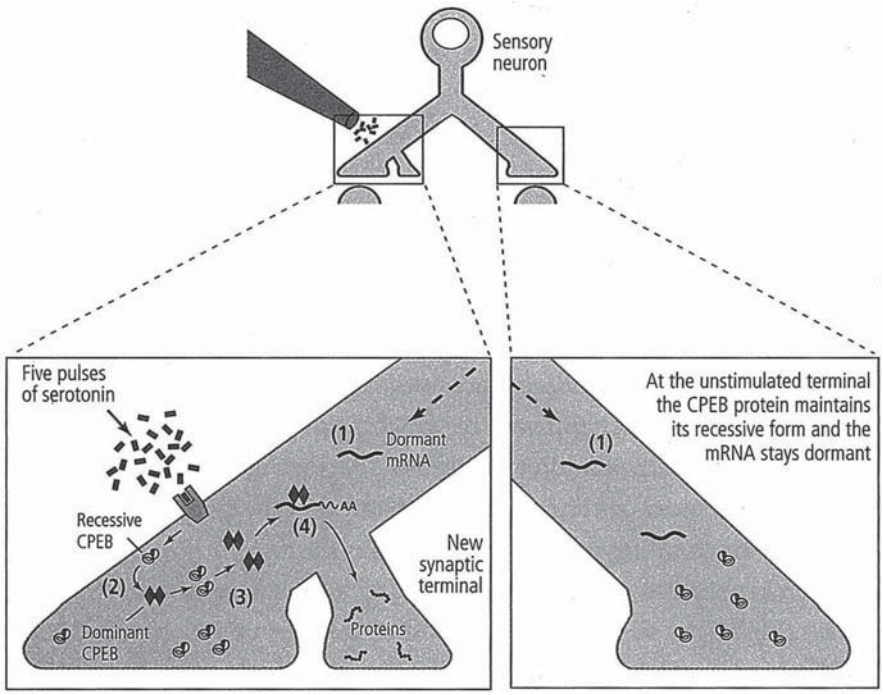

Fig. 9.3 Role of repeated stimulation in memory formation. (From Kandel, 2006, p. 274, reprinted with permission)

does not result in replication of the foreign prion, but rather it converts the existing noninfectious prion into the infectious conformation. In the case of CPEB, it becomes infectious when stimulated with serotonin. The infectious form of CPEB replicates itself and maintains local protein synthesis at the synapse. It perpetuates synaptic facilitation and thus long-term storage of memory.

Repetition is in general necessary for long-term memory. So-called flashbulb memory may occur if an event is highly emotionally charged and causes a massive influx of MAP kinase and protein kinase A into the nucleus to activate all CREB-1 protein and inactivate all CREB-2, thus directly creating a long-term memory.

While implicit memory can be stored in any synapse, basal ganglia and the cerebellum seem to be particularly involved in its storage in mammals.

9.1.2 Explicit Memory

Storage of explicit memory, unlike implicit memory that can be achieved at the level of a single synapse, involves the brain as consciousness and language involves the integrative function of the brain.

The sensory and association cortices, speech centers, the limbic system, especially hippocampus and amygdala, and the entorhinal cortex are intimately involved in explicit memory. Among the structures, hippocampus is considered to be the brain structure that is involved in consolidating short-term memory into long-term memory. Attention, mediated by the neurotransmitter dopamine, is necessary for explicit memory to occur. BDNF is considered to be essential in maintaining long-term explicit memory (Bekinschtein et al., 2008).

In animals, a *spatial map* develops when they enter a new environment, i.e., the hippocampus develops a multisensory representation of the new environment. The spatial map was destabilized and did not last long when protein kinase A was blocked, showing that it is memory dependent. Such a representation may be a form of explicit memory in animals (Kandel, 2006). The spatial map was destabilized when dopamine blockers were administered and enhanced when dopamine receptors were activated, indicating the necessity of attention.

Repeated rapid stimulation of neuronal pathway to the hippocampus leads to strengthening of the connection for hours and days. This type of synaptic facilitation is called long-term potentiation (LTP) (Bliss and Lomo, 1973). Glutamate is the principal excitatory neurotransmitter in the brain. Glutamate acts on both the AMPA and the NMDA receptors in the hippocampal neurons. The AMPA receptor mediates normal synaptic transmission, responding to potential from presynaptic neuron. When the postsynaptic neuron is stimulated repeatedly and rapidly, the AMPA receptor powerfully depolarizes the cell membrane allowing an ion channel in the NMDA receptor to open, allowing calcium ion influx (Kauer et al., 1988; Lynch et al., 1988). Calcium then acts as a second messenger akin to cyclic AMP discussed above, triggering activation of kinases which in turn activate CREB resulting in structural change of the neuron associated with LTP. Rhythmic bursting activity is highly effective in inducing LTP and the endogenous hippocampal theta rhythm may play a role in LTP induction in vivo (Lynch et al., 1990).

In LTP of rat hippocampal neurons, dopamine rather than serotonin (as in *Aplysia*) modulates the prion-like CPEB protein (CPEB-3) that results in perpetuation of the structural change at the synapse.

9.1.3 Learned Fear

Conditioned fear response is a basic learned response that involves long-term memory. The brain has to remember the stimulus associated with fear to elicit the response.

When a tone is paired with an electric shock in the rat, the tone travels through the auditory nerve to the medial geniculate body of the thalamus. The signal is then carried by two separate pathways: one goes directly to the lateral nucleus of amygdala, and another pathway goes to the auditory cortex first, then to the lateral nucleus of amygdala.

The electric shock activates pain fibers that terminate in the somatosensory thalamus. From the thalamus, there again emerge two separate pathways, one directly to the lateral nucleus of amygdala, the other through the somatosensory cortex to the same nucleus.

The existence of two separate pathways for sensory input to amygdala, one through the cortex and another bypassing it, indicates that unconscious evaluation of fearful stimulus precedes conscious evaluation of it (Kandel, 2006). When the neurons in the lateral nucleus are sufficiently stimulated, they send impulses to the central nucleus, which in turn send signals to hypothalamus, limbic system, and the cortex that result in the autonomic, endocrine, and behavioral fear response. Brain-derived neurotrophic factor (BDNF) plays an important role in synaptic plasticity. Calcium influx through NMDA receptors and voltage-dependent calcium channels, which occurs in the lateral nucleus during fear conditioning, activates protein kinase A and Ca^{2+}/calmodulin-dependent protein kinase IV. Each induces phosphorylation of CREB, which binds to the BDNF promoter, leading to BDNF expression in the lateral amygdala and contributes to fear memory consolidation (Monfils et al., 2007). Repeated stimuli of this sort result in long-term potentiation in the circuits from thalamus to lateral nucleus of amygdala and from the lateral nucleus to central nucleus, i.e., a conditioned reflex has been formed.

A gene encoding gastrin-releasing peptide (GRP) has been found to be highly expressed both in the lateral nucleus of the amygdala and in the regions that convey fearful auditory information to the lateral nucleus. GRP receptor (GRPR) is expressed in GABAergic interneurons of the lateral nucleus. GRP excites these interneurons and increases their inhibition of principal neurons. GRPR-deficient mice showed decreased inhibition of principal neurons by the interneurons, enhanced long-term potentiation (LTP), and greater and more persistent long-term fear memory. By contrast, these mice performed normally in hippocampus-dependent Morris maze. GRP and its neural circuitry seem to operate as a negative feedback regulating fear and establish a causal relationship between GRPR gene expression and LTP, and amygdala-dependent memory for fear (Shumyatsky et al., 2005, 2002).

9.1.4 Learning Safety

What happens in the brain when an animal learns that certain signals denote safety? Rogan et al. gave electric shock to mice only during periods when a tone was *not* on, that is, when the mice heard the tone, it meant it was safe. Thus, the conditioned stimulus (tone) came to signify a period of protection, reducing fear responses and increasing adventurous exploration of a novel environment. Mice turned on the tone when given the opportunity. Thus, conditioned safety involves a reduction of learned and instinctive fear, as well as positive affective responses. Concurrent electrophysiological measurements revealed a safety learning-induced long-lasting depression of tone-evoked activity in the lateral nucleus of the amygdala, consistent

with fear reduction, and an increase of tone-evoked activity in a region of the striatum involved in positive affect, euphoric responses, and reward (Rogan et al., 2005). Thus, the memory of positive events and feelings are also stored in neurons through LTP and associated structural change in neurons in different pathways of the brain.

The tone-sensitive neurons in the thalamus and the neurons in the lateral nucleus of amygdala both have connections with the striatum, and both convey information concerning safety. Striatum in turn is connected with many areas of the brain including the cingulate gyrus that inhibits amygdala. Thus stimulation of the striatum may also decrease activation of amygdala and thus fear response.

9.1.5 Working Memory

Working memory involves the temporary storage and manipulation of information necessary for the task at hand. Baddeley and Hitch proposed a multicomponent model consisting of four subsystems. The first is concerned with verbal and acoustic information, the phonological loop; second, the visuo-spatial sketchpad providing its visual equivalent, while both are dependent upon a third attentionally limited control system, the central executive, and a fourth subsystem, the episodic buffer (Baddeley, 2003; Baddeley and Hitch, 1974).

The *central executive* is the master unit that is responsible for information integration and coordination of the subordinate systems and is considered to be largely a function of the dorsolateral prefrontal cortex and its connections (Baddeley, 2003; Goldman-Rakic et al., 2004; Kondo et al., 2004). The central executive directs attention to relevant information and suppresses irrelevant information and inappropriate actions and coordinates cognitive processes for competing tasks.

The *phonological loop* stores phonological or sound-related information in a temporary store and prevents its decay by continuously refreshing it through a subvocal rehearsal system. The phonological loop not only maintains the sound information but also registers visual information within the store provided the items can be named. Different parts of the Broca's area seem to be involved in the storage and subvocal rehearsal systems. The verbal working memory seems to be largely localized in the left hemisphere (Baddeley, 2003).

The *visuo-spatial sketchpad* stores visual and spatial information. It can be used, for example, for constructing and manipulating visual images and for the representation of mental maps. The sketch pad may be subdivided into a visual subsystem (dealing with shape, color, texture, etc.) and a spatial subsystem (dealing with location). The spatial system seems to be localized more in the right hemisphere (Smith and Jonides, 1997).

PET studies show that separable components may be responsible for the passive storage of information and the active maintenance of information, with the storage component being localized more in the back of the brain, and the maintenance component in the front (Smith and Jonides, 1997).

The *episodic buffer* is considered to be a limited capacity system that depends heavily on executive processing, but which differs from the central executive in

being principally concerned with the storage of information rather than with attentional control. It binds together information from a number of different sources into chunks or episodes. In this buffer, information from different modalities can be combined into a single multifaceted entity. Baddeley proposed that this may underpin the capacity for conscious awareness (Baddeley, 2000, 2001). The episodic buffer seems to be multimodal in function. The formation of unitary multidimensional representations in the episodic buffer seems to engage posterior neural networks, but maintenance of such representations is supported by frontal networks. The hippocampus and prefrontal cortex play important roles in the representations in the episodic buffer of working memory (Rudner and Ronnberg, 2008; Yoon et al., 2008).

Working memory is important in psychiatry as it is impaired in various psychiatric conditions including schizophrenia and mood disorders. In schizophrenia, there is an overproduction of dopamine D2 receptors that is associated with psychotic symptoms and a reduction in D1 receptors. There seems to be a direct relationship between the prefrontal dopamine function and the integrity of working memory, suggesting that insufficient D1 receptor signaling, and thus reduction in cyclic AMP and glutamatergic transmission, resulting in cognitive deficits. Working memory deficits can be ameliorated by treatments that augment D1 receptor stimulation (Goldman-Rakic et al., 2004).

In depression, there is often cognitive impairment and a reduction in the size of the hippocampus, especially after repeated bouts of severe depression. Antidepressants and ECT all have the effect of increasing neurogenesis in the dentate nucleus of the hippocampus. The newly generated neurons are particularly sensitive to LTP (Pittenger and Duman, 2008; Sahay and Hen, 2007).

9.2 Evolution of Memes in the Brain and the Brain Code

Once learned stuff has been stored in the brain by forming neuronal synaptic connections through LTP, what happens to the memory? We know that memory tends to decay over time, and some memories are better preserved than others. We have seen that emotionally charged events may become instantly fixed in memory (flashbulb memory) while boring factual information may require a long series of repetitions to become long-term memory.

Hippocampus is the main brain site for the conversion of short-term memory into long-term memory as long-term memory does not form without it. Hippocampus is also one area of the brain where chronic stress reduces the number of neurons and their connections, and where neurogenesis occurs in adulthood (Drew and Hen, 2007; Gould et al., 1997; Pittenger and Duman, 2008; Sahay and Hen, 2007).

In the mouse hippocampus, different groups of neurons respond to different stimuli, such as shake or air blow. Such identification of network-level functional coding units, termed neural cliques, has allowed real-time patterns of memory traces to be digitized (Lin et al., 2007). For example, Lin et al. were able to express the memory code associated with an experience in binary code based on a predefined sequence

of clique assembly (general startle, air blow, drop, shake, air subcontext, drop subcontext): the activation code 110010 corresponding to the internal representation of the air blow in context A, 110000 to air blow in context B, 101000 to drop elevator A, 101001 to drop elevator B, and 100100 to shake. See Fig. 9.4.

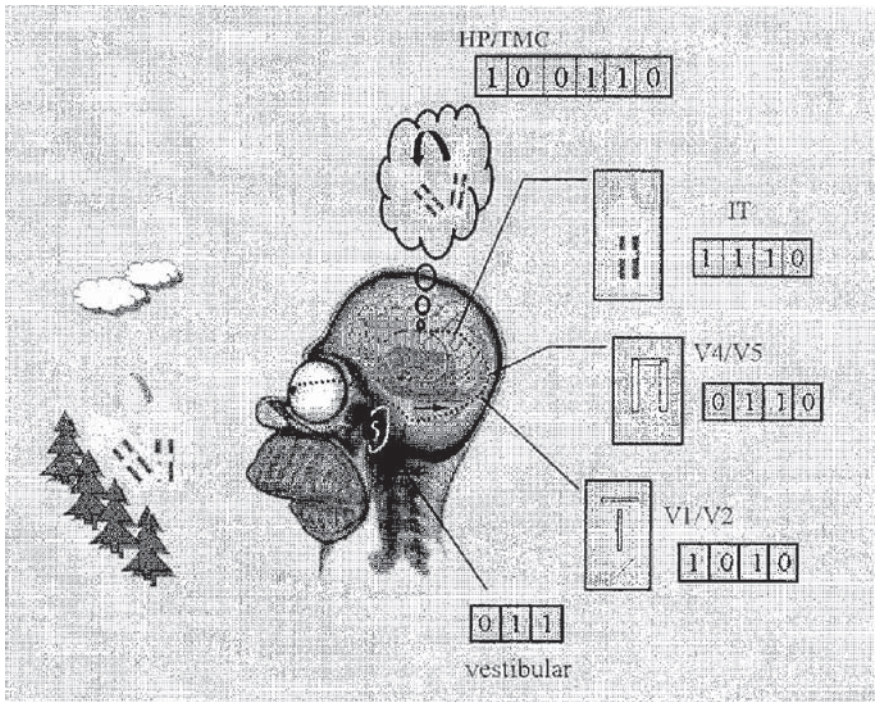

Fig. 9.4 Neural clique code-based real-time information processes in the brain. Through a series of hierarchical-extraction and parallel-binding processes, the brain achieves coherent internal encoding and processing of external events. For example, when a person experiences a sudden earthquake, neural cliques in his primary visual cortex encode the decomposed features about edge orientation, movement, and eventually shapes of visual objects, whereas the neural cliques in the vestibular nuclei detect sudden motion disturbances. As information is processed along its pathways into deeper cortex such as the inferior temporal cortex (IT), neural cliques begin to exhibit complex encoding features such as houses. By the time it reaches high association cortices such as the hippocampus (HP) and temporal medial cortex (TMC), the neural clique assembly encodes earthquake experience and its location, with a selective set of "what and where" information. At this level, abstract and generalized information such as semantic memories of "the earthquake is dangerous and scary" have emerged. As information is further processed into other cortical regions involving decision making and motor planning, a series of phased firing among various neural clique assemblies lead to adaptive behaviors such as screaming and running away from the house, or hiding under a dining table. As illustrated, the activation patterns of neural clique assemblies in each brain region can be also converted into a binary code for universally comparing and categorizing network-level representations from brain to brain. Such universal brain codes can also allow more seamless brain–machine interface communications. (Figure and legend reprinted with permission from Elsevier (Tsien, 2007))

Any given episodic event is represented and encoded by the activation of a set of neural clique assemblies that are organized in a categorical and hierarchical manner. This hierarchical feature-encoding pyramid is composed of the general feature-encoding clique at the bottom, sub-general feature-encoding cliques in the middle, and highly specific feature-encoding cliques at the top. Tisen states that this hierarchical and categorical organization of neural clique assemblies provides the network-level mechanism the capability of not only achieving vast storage capacity, but also generating commonalities from the individual behavioral episodes and converting them to the abstract concepts and generalized knowledge that are essential for intelligence and adaptive behaviors. The conversion of activation patterns of the neural clique assemblies to strings of binary codes may permit universal categorizations of the brain's internal representations across individuals and species. Such *universal brain codes* can also potentially facilitate the unprecedented brain–machine interface communications (Tsien, 2007).

Tsien states that the binary brain code differs from the genetic code in several aspects as follows:

1. Uninheritable: genetic code is directly inherited through reproduction, while brain code is formed through experience or imitation.
2. Self-organizing: genetic codes are like blue prints, while brain codes are dynamical and self-organizing based on connections.
3. Variable sizes: genetic codes are fixed in size in each individual and species, while brain codes are variable in size limited only by the network capacity determined by the convergence or divergence of connections and individual's experiences.
4. Modifiable: genetic code remains the same within an individual unless mutated, while membership of individual neurons in a neural clique depends on synaptic connections based on experience or disease states (Tsien, 2007).

Such universal brain codes might be exactly what we know as memes (or protomemes for animals that lack imitation or communication skills). While the brain code is not inheritable through biological reproduction, it can spread through imitation, language, and electronic means, and thus can be reproduced in other brains. Thus, memes reside as brain codes of neural cliques in the brain. Outside the brain, memes may reside in computers as binary codes on silicon, as patterns of ink in the print media, or streams of radio waves.

Edelman has shown that clusters of neurons in the brain are subject to Darwinian natural selection. Edelman's theory of neuronal group selection posits that neuronal selection occurs in three facets: (1) Developmental selection – during early phases of neural development, random variations of synaptic connections exist, and groups of neurons that are wired together fire together. (2) Experiential selection – the groups of neurons that are formed during the first phase are selected by experience, i.e., by reinforcement or nonreinforcement, throughout life. The reinforcements are repeated firings that form strengthened connections such as LTP, facilitated by emotional arousal. (3) Reentry – large numbers of local and long-distance reciprocal

neural connections are established. They provide ongoing recursive interchange of parallel signals among brain areas that serves to coordinate the activities of different brain areas in space and time (Edelman, 1987, 1993; Edelman, 2004). According to Edelman, neuronal groups connected by reentrant interactions are the selectional units in higher level brains (Edelman, 2004). *These neuronal groups might be identical or similar to the "neural cliques" that fire together as described above and may represent memes.*

Neuronal group selection is a Darwinian natural selection that occurs during the lifespan of an animal and is dependent on reinforcement. Lack of reinforcement usually results in reduction in synaptic connections, thus rendering the group silent or inactive.

It is clear, then, that if memes can be represented as binary codes of excitation of "neural cliques", and neuronal groups that are connected by parallel interactions as described by Edelman undergo Darwinian natural selection, then *memes must undergo Darwinian natural selection in the brain*. *Neuronal groups may be reinforced by signals (reentrance) from other similarly firing neuronal groups (forming memes) and thus gain survival advantage.* One might say that neurons thrive on memes. When a competing meme becomes dominant, neural cliques underlying it are enhanced, i.e., better fed, with more synapses.

Thus, some memes will become dominant with repeated exposure and rehearsal and proliferate, i.e., recruit other neuronal groups; others will become dormant, not forming new connections or recruiting others. The process of reentry resulting in new parallel connections may be seen to be a process of replication of the meme, a prion-like replication by contact through synaptic and/or dendritic connection. This is not to imply that one neuron serves only one meme. In fact, a neuron has many connections and may be a component of a number of different memes and memetic connections.

Meme replication in the brain, therefore, does not involve reproducing new neurons, but rather occurs through recombination of component memes in existing neuronal groups. Such replication may occur through meme-processing mechanisms such as cognition, often stimulated by the entry of new memes into the brain.

The brain, in my view, is more like the Internet than one computer, with redundant storage and constantly changing connections and storage, in which memes are constantly created, propagated, combined, disintegrated, mutated, and evolved. Like the Internet, there are many interconnected processing centers that execute these functions. Some of these functions may involve a threshold number of processing units and reach consciousness, others without reaching consciousness. Just like information on the Internet, some memes stay dormant and others become activated and replicated.

Dreaming may be an important meme-processing brain state. Visual dreams occur mostly during the rapid eye movement sleep (REM), during which there is autonomic arousal and motor inhibition. During this period, impulses arising from brain stem (PGO spikes) reach sensory and association cortex through the thalamus.

Winson postulates that REM might be like off-line processing in computers. In this model, the task of associating recent events to past memories is accomplished while the animal is asleep. This spares the frontal cortex from having to process new information and integrate it simultaneously, allowing a more leisurely integration during sleep (Winson, 1985).

Reiser postulates that these impulses will readily activate neural circuits with relatively low excitatory thresholds, i.e., those circuits that retained memories of meaningful experiences to which emotions are attached and connected to current life problem (Reiser, 1991). These circuits would be those that represent significant memes stored during the day. During dreaming, then, the newly introduced memes find new connections with already stored memes, may combine with some forming memeplexes, may awaken others from a dormant state, or may become dormant or be simply discarded.

In addition to newly introduced memes finding connections with stored memes during the dreaming state, dreams may also represent the processes of existing memes finding new combinations and connections that are significant enough to reach consciousness. Thus, in dreams, we may have a glimpse of the memes struggling with each other, constantly making and breaking new alliances, configurations, and reproductions within our brain.

In the process of human evolution, the brain's capacity to contain memes improved and so did the pace of evolution of memes within the brain as learned entities. There is, however, a limit to how large human brain can become given the genes of mammalian evolution. Cesarean sections are already commonly needed because of the increasing size of the fetal brain. Memes within one brain die with the brain. Memes had to find ways of sending copies outside of the brain in a reliable way and also to reside outside of the brain until it can infect other brains. This will be the topic of the next chapter.

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