

MEMORY IN FOUR DIMENSIONS

Introduction

Memory is the ability to store, retain, and recall information. Memory of personal past experiences of a particular time and place ("what", "where", and "when") with reference to the person as a participant is known as episodic memory (Munoz-Lopez, 2010; Schacter et al, 2011; Tulving, 1985, 2001, 2002). Such memory is normally thought of as being three dimensional. However, utilizing relativistic principles, episodic memory can be shown to be four-dimensional (three dimensions of space, one dimension of time).

Declarative (explicit) memory refers to memory which can be consciously recalled (Tulving, 1983; Ullman, 2004). There are two categories of declarative memory (Graf & Schacter, 1985; Tulving, 1972; Tulving & Schacter, 1990). Semantic memory is a structured record of facts, concepts, and skills that is independent of personal experience. Episodic memory is a record of personal past experiences. Episodic memory may provide basic support for semantic memory and semantic information may be derived from accumulated episodic memory. Episodic memory may be thought of as a map that ties together items in semantic memory. Episodic memory and semantic memory each represent different parts of a complete picture. As such, something that affects episodic memory can also affect semantic memory. Anterograde amnesia is an impairment of declarative memory that affects both episodic and semantic memory (Howard & Kahana, 2002; Tulving & Markowitsch, 1998).

Episodic memory requires no training and is mostly automatic or incidental. However, as will be seen, the encoding of episodic memory is associated with consciousness and can even be voluntarily directed by consciousness. The retrieval or recall of episodic memory requires conscious effort (Munoz-Lopez et al, 2010). Conscious recollection is required to demonstrate episodic memory (Tulving, 1983). Hence both the encoding and recall of episodic memory is associated with consciousness. This is interesting as it can be shown that consciousness itself is also similarly organized in four dimensions at any one time.

Gabriele and Kao (2007) found that the formation of new declarative memories relies on both the hippocampus and parahippocampus. The hippocampus and surrounding structures in the medial temporal lobe of the brain are specifically most important in declarative memory (Eichenbaum, 2001). Eichenbaum (2001) found that the ability to encode, retain, and recall episodic memories is highly dependent on the hippocampus (the

hippocampus acts as a memory space). Episodic memory stores context-rich information about everyday events and depends on the hippocampal formation (entorhinal cortex, subiculum, presubiculum, parasubiculum, hippocampus proper, and dentate gyrus-Munoz-Lopez et al,2010). Lesions that include the hippocampus, amygdala, and adjacent entorhinal and posterior parahippocampal cortices impair episodic memory in humans, with intact perception and working memory (Mishkin,1978;Munoz-Lopez et al,2010;Scoville & Milner,1957). The perirhinal cortex receives most of its input from visual areas of the inferior temporal cortex (Suzuki & Amaral,1994a) and sends this information to the entorhinal cortex (Insausti et al,1987a; Suzuki & Amaral,1994b), from where the information accesses the hippocampus (Witter & Amaral,1991). The inferior temporal cortex is closely connected to the inferior parietal cortex, probably the most important area of multimodal processing, which is involved in attention, perception, working memory, and conscious experience (Sieb,2004,2007,2011,2013). There are return projections from the hippocampus to the entorhinal cortex primarily, but also directly to the perirhinal cortex (Insausti & Munoz,2001;Lavenex et al,2002;Witter & Wouterlood,2002;Munoz & Insausti,2005). These connections may be critical for the consolidation of episodic memory for the long term in the cerebral cortex (Munoz-Lopez et al,2010). These studies indicate the main flow of information underlying episodic memory.

The formation of new episodic memories requires the medial temporal lobe of the brain (which includes the hippocampus). Without the medial temporal lobe, one is able to form new procedural memories, but cannot remember (episodic memories) the events in which they arose. The prefrontal cortex (particularly in the left hemisphere) is also involved in the formation of new episodic memories. Patients with damage to the prefrontal cortex can learn new information, but tend to do so in a disordered fashion (Janowsky et al,1989). The lateral prefrontal cortex may be essential for remembering the contextual details of episodic memory (Gabriele & Kao,2007). The prefrontal cortex may help organize information for more efficient storage or underlie semantic strategies which enhance encoding, such as thinking about the meaning of the material or rehearsing it in working memory (Gabrieli et al,1998). There is disagreement on the length of time episodic memories are stored in the hippocampus. Some believe episodic memories always rely on the hippocampus. Others believe the hippocampus only stores episodic memories for a short time, after which they are consolidated to the neocortex. The latter view is strengthened by evidence that neurogenesis in the adult hippocampus may ease

the removal of old memories and increase the efficiency of forming new memories (Deisseroth et al,2004). The amygdala is involved in strengthening memory of emotionally-arousing stimuli, but is not required for memory of emotionally-neutral stimuli (Adolphs et al,1997;Babinsky et al,1993). It is much easier to remember an emotionally-charged event than one that is not emotionally-charged.

A central feature of episodic memory is that it is a combination of information from different sensory modalities (olfactory, somatosensory, auditory, and visual). Episodic memory is multimodal. Studies show that although some sensory-specific information reaches the medial temporal cortex directly (primarily olfactory and visual, but also to a lesser extent, somatosensory and auditory), the great bulk of incoming information originates from polymodal areas of the neocortex (Mohedano-Moriano et al,2007), such as the inferior parietal cortex, providing episodic memory with rich complex contextual information. Episodic memory is based on context and its retrieval often depends on context.

Tulving (1983,2002) describes episodic memory as a temporally-dated record of a person's experiences. Episodic memories include times, places, associated emotions, and other who, what, when, where, and why information that can be explicitly stated (Schacter et al,2011). It allows one to figuratively travel back in time to experience again events that took place. All this information forms a context for the memory. Conway (2009) attributes nine properties to episodic memory: (1) it is a summary record of sensory-perceptual-conceptual-affective processing, (2) it retains patterns of activation/inhibition over long periods, (3) it is often represented in the form of (visual) images, (4) it always has a perspective (field or observer, frame of reference), (5) it represents short time slices of experience, (6) it is represented on a temporal dimension roughly in order of occurrence, (7) it is subject to rapid forgetting, (8) it makes autobiographical remembering specific, and (9) it is recollectively experienced when accessed. These properties arise because episodic memory utilizes a discrete type of information processing and is associated with consciousness. The third property may be a consequence of the four-dimensional organization of episodic memory.

In recent years, our understanding of episodic memory has undergone a radical revision, with a transition from a system directed exclusively to the past to a system also oriented to the future. Studies indicate there is a link between the

retrieval of personal past events and the construction of future imaginary events. Schacter and Addis (2007a,b,2009) highlight the role of episodic memory in the construction of future events. This adaptive function of episodic memory extracts components of the past, then assembles and recombines them to remember the past and to imagine the future (Hardt et al,2010; Howe,2011;Schacter et al,2011). Hassabis and Maguire (Hassabis et al,2007a;Hassabis & Maguire,2007,2009) argue for a process of "scene construction" that links memory and imagination. Since episodic memory appears to have a four-dimensional organization, this reconstruction process may be even more intricate and fascinating than "imagined".

Since episodic memory encoding and recall is associated with consciousness, the next few sections describe the nature of consciousness and conscious experiences and how they are associated with episodic memory. How the four-dimensional organization of consciousness and episodic memory evolves is then discussed. This entails examination of Einstein's special and general theories of relativity, spacetime, and the concept of invariant spacetime intervals. Components of episodic memory (sensory memory, working memory, short term memory, LTP, LTD, STDP, homeostatic synaptic regulation and plasticity, and long term memory) are subsequently described in great detail.

Consciousness

Consciousness is a state of awareness known as the waking state. The encoding and recall of episodic memory is associated with consciousness (episodic memory encoding and recall occurs only when one is awake or conscious). Consciousness arises and is maintained by a particular system in the brain called the reticular activating system. The reticular activating system and the cerebral cortex are necessary parts of a system that maintains consciousness (Hannaman,2005;Young,2009). The reticular activating system originates in the upper brainstem reticular core and projects through the intralaminar thalamic nuclei to the cerebral cortex to mediate arousal, attention, and consciousness, ie. the waking state (Evans,2003;Hannaman,2005; Kinomura et al,1996;Reiner,1995;Steriade,1995,1996;Young,2009). The noradrenergic locus coeruleus, the mesencephalic reticular formation, the cholinergic nucleus basalis of Meynert, the dorsal hypothalamus, the intralaminar thalamic nuclei, and the tegmentum make up the reticular activating system (Afifi & Bergman,1986;Best,2010;Hannaman,2005;Kinomura et al,1996;Rang, 2003;Steriade et al,1990;Thierry et al,1990;Vertes,1990). Bilateral damage to the intralaminar thalamic nuclei produces lethargy or somnolence (Steriade,1996). Damage to the reticular

activating system results in coma (Daltrozzo et al,2009,2010; Liversedge & Hirsch,2010;Young,2009). Partial destruction or inhibition of the reticular activating system results in a partial loss of consciousness known as an acute confusion state or delirium (Rull,2011). The function of the reticular activating system is modulated by its adrenergic and cholinergic components (Burlet et al,2002;Evans,2003;Garcia-Rill,1997; Garcia-Rill et al,2007;Reiner,1995). Drugs or activities which enhance adrenergic and cholinergic action in the brain also enhance episodic memory (Apud et al,2007;Dunbar et al,2007;Gron et al,2005).

Information Processing

Discrete and continuous processing are two distinct types of information processing that occur in organized systems. Discrete processing and continuous processing are differentiated by their very different physical mechanics and behavior. Each type has its advantages and disadvantages. One type appears to be involved in the production of consciousness, while the other type is involved in the production of conscious experiences and episodic memories.

Continuous Processing

Continuous processing is constant, consistent, and uninterrupted (Henthorn,2013;Perry et al,1997;Ricketts,2013). There is a seamless flow from input to output. Continuous processing may be so fast as to appear almost immediate or instantaneous. This is exemplified by the extremely fast processing of word processors and the regulation of human vital functions (breathing, heart rate, etc.). Continuous processing is sensitive, accurate, stereotyped, consistent, predictable, and reliable. Thermometers, thermostats, barometers, clocks, watches, engines, machines, human reflexes, and production lines use continuous processing. Continuous processing is context-independent. It occurs in a stereotyped predictable manner regardless of the surrounding conditions. Continuous processing is not labor-intensive. Human vital functions are regulated continuously, without interruption or fatigue, throughout life. Clocks and watches operate continuously and accurately for years, without maintenance. Continuous processing is inflexible and invariable. It does not give rise to anything new or novel. Nonlinearity has no place in continuous processing, ie. the output is always proportional to the input and precisely as predicted. Negative feedback may be utilized in continuous processing to regulate rate of flow, detect errors, assess

trends, and determine rate of change of errors (Henthorn,2013). Continuous processing may vary in level.

Consciousness arises relatively instantly or immediately upon awaking from sleep or anesthesia. The generation of consciousness is constant, continuous, consistent, reliable, uninterrupted, accurate, stereotyped, inflexible, invariable, free from interference, and predictable. It is context-independent. Small perturbations (psychoactive drugs and chemicals, anesthetics, toxins, fatigue, hypnosis, meditation, sleep, diseases) can change the level of consciousness. The production of consciousness is not labor-intensive. The reticular activating system is relatively non-specific and context-independent, as any type of sensory stimulation may generate consciousness. The reticular activating system therefore appears to be a continuous processing system operating to generate consciousness (the waking state). Consciousness appears to set the stage for conscious experience and episodic memory.

Discrete Processing

Discrete processing occurs in stages (Dawson,2013) and is characterized by distinct separate unit production (Edwards, 2013). Discrete processing is characterized by production of a series of distinct separate identifiable states. Processing occurs over distinct (discrete) intervals or periods of time, called integration periods (episodes, epochs, or packets). Each integration period represents a separate distinct (discrete) identifiable state of the system. Integration periods may be of varying lengths of time and occur serially in a given system. Discrete processing is slower and more labor-intensive than continuous processing. Appreciable interference may occur, as input might backup or accumulate, because of the interpolation of integration periods. Information can interact and be manipulated over integration periods. Nonlinearity therefore is an integral part of the processing. This makes discrete processing variable, flexible, and unpredictable. Information is integrated in new or novel ways, resulting in the emergence of new or novel results. Hence the results of discrete processing might be said to emerge. In a given system, one period of processing ends before another period of processing begins. Thus discrete processing occurs in a sequential or serial manner, one period of processing succeeding another. The serial nature of discrete processing would be expected to slow processing in general and create a bottleneck. One period of processing may also prime subsequent periods of processing.

Episodic memory, as its name implies, consists of a series of distinct (discrete) separate identifiable explicit states (episodes). Episodic memories are self-generated, arise rapidly in recurrent systems, take time to form (integration periods), have a prolonged duration, are seamless, structurally-complex, ineffable, transparent, bounded, unified and coherent, informative, serial, limited in capacity, subject to interference, new or novel, variable, flexible, project outwards, explicit, gain access to other systems, and arise from attention. All these properties suggest that episodic memories develop in a discrete processing system. Conscious experiences, which make up the content of consciousness, have the same properties (Baars,1988;Koch,1998;Libet,1983,1985;Sieb,2004,2007,2011,2013;Tononi & Edelman,1998), as episodic memories. Both conscious experiences and episodic memories therefore appear to arise from a similar type of discrete processing.

Neglect

Neglect syndrome may arise with damage to the inferior parietal cortex (Joseph,1990,2000;Mattingley,1999;Prinz,2003,Lecture at *Towards A Science Of Consciousness (TASOC) 2012 Conference*). Neglect syndrome is a deficit in awareness (conscious experience) of one side of space that occurs as a result of brain damage (Husain,2008;Unsworth,2007). Neglect appears to be caused by an inability to pay proper attention to sensory stimuli (Husain,2008;Unsworth,2007). Neglect is most profound with damage to the right cerebral hemisphere with the deficit to the left side of space (Husain,2008;Unsworth,2007). Left hemisphere damage may produce a less prolonged and long-lasting neglect of right space (Husain,2008;Kim et al,1999). Neglect is classically associated with lesions of the right posterior parietal cortex, particularly of the right temporoparietal junction and inferior parietal cortex (Husain,2008;Mattingley,1999;Vallar & Perani,1986). Isolated lesions of the right frontal lobe have also been associated with neglect of left space (Husain & Kennard,1996). Severe left unilateral inattention and neglect is seen with massive lesions to the right frontal lobe of the brain (Joseph,1988a,1988b,1990,2000). Subcortical lesions, without involvement of the overlying cortex, can lead to neglect (Hillis et al,2002;Hillis et al,2005). Damage to white matter pathways connecting posterior and frontal cortical areas has also been implicated in neglect (Bartolomeo et al,2007;Thiebaut de Schotten et al,2005). Loss of dreaming (a type of conscious experience) can occur with parietal cortex damage (Solms,M.,In "*What Are Dreams?*",KSPS Nova

TV Program,2009). It is also interesting to note that episodic memory does not occur on the affected side during neglect. Thus the neglect syndrome suggests that the connections between the inferior parietal cortex and frontal cortex are quite important in attention, conscious experience, and episodic memory.

Feedback and Conscious Experiences

An increasing number of investigations have found that feedback connectivity between the frontal lobes and parietal lobes of the brain is required to generate conscious experience (Boehler et al,2008;Crick & Koch,1995;Fahrenfort et al,2007;Lamme & Roelfsema,2000;Ro et al,2003;Tononi & Koch,2008). Crick and Koch (2003) and Hudetz and coworkers (2006) determined that conscious experience depends on neuronal coalitions spanning the posterior sensory cortices and the executive areas of the prefrontal cortex. Laplant and coworkers (2005) demonstrated a reduction in frontal activation in anesthetized animals that was normally present in waking animals. Demertzi and coworkers (2013) and Lapitskaya and coworkers (2013) found that external sensory awareness is an emergent property dependent on cortical-cortical interconnections in a widespread frontal-parietal network. Activity in this network was reduced during anesthesia, coma, unresponsive wakefulness syndrome (vegetative state), and minimally conscious states. Imas and coworkers (2005) found recurrent feedback from anterior to posterior brain areas was suppressed earlier in anesthetized animals than feed forward information transfer. It has been found that anesthetics suppress mainly parietal cortex feedback connectivity, but not parietal cortex feed forward connectivity (Avidan et al,2011;Ku et al,2011;Lee et al,2009). This is reversed upon awakening. Mashour (Consciousness in the operating room,Lecture at *TASOC* 2012 Conference) concluded that the parietal cortex is affected much more than frontal areas by anesthetics, that conscious experience is likely a cortical-cortical feedback interaction, and that conscious experience may be governed by this feedback interaction.

Perception and Attention

Perception and focal attention are necessary for conscious experience (Rowlands,2002;Velmans,1999). The inferior parietal cortex receives highly processed input from somesthetic, visual, and auditory association cortex, the frontal lobes, and other higher-order assimilation areas throughout the neocortex (Bogarts,1997;Bruce et al,1986;Burton & Jones,1976;John,2009; Jones & Powell,1970;Joseph,1990,2000;Petrides & Pandya,2007;

Seltzer & Pandya,1978;Zeki,1974). The inferior parietal cortex can simultaneously analyze visual, auditory, and somesthetic information, respond to visual stimuli of any size, shape, or form, and has neurons with visual receptive properties that span almost the entire visual field (Bruce et al,1982,1986;Hyvarinen & Shelepin,1979;Joseph,1990,2000). The inferior parietal cortex is involved in the creation and assimilation of cross-modal associations (auditory, visual, and somesthetic equivalents of objects, events, ideas, actions, feelings-Joseph,1990,2000). This is perception. Episodic memory is also multimodal in composition and the hippocampal formation involved in the encoding of episodic memory receives primary input from the inferior parietal cortex. Damage to the left inferior parietal cortex may cause various disorders that involve perceptual deficit (which may appear to be a memory deficit)-anomia, object and finger agnosia, acalculia, most forms of apraxia, agraphia, left-right disorientation, pure word blindness, alexia, conductive aphasia, disruption of sequential-grammatical relationships, disruption of spatial-sequential ability, impairment of visual-spatial functioning, impairment of temporal-sequencing ability, disruption of the performance of skilled temporal-sequential motor acts, and the impairment of logic and grammar (Benson et al,1973;Heilman,1973,1979;Hechaen & Albert,1978;Joseph,1990,2000;Luria,1980;Sauguet et al,1971; Straub & Geschwind,1983;Vignolo,1983). Dressing apraxia and constructional apraxia may occur with right inferior parietal cortex damage (Hier et al,1983;Mehta et al,1987;Joseph,1988a, 1990,2000). The frontal lobes, especially the right frontal lobe, and the parietal lobes have great attention capacity (Desmedt,1977;Dimond,1976,1979;Hielman & Van Den Abell,1979, 1980;Joseph,1982,1986a,1988a,b;Tucker,1981). The frontal cortex and the inferior parietal cortex therefore appear to be involved in perception and focal attention, the two processes necessary for the formation of conscious experiences (and episodic memories).

It appears from the preceding sections that both conscious experience and episodic memory depend on the inferior parietal cortex. The inferior parietal cortex accesses the hippocampus via the perirhinal cortex and entorhinal cortex in the encoding of episodic memory and the hippocampus accesses the entorhinal cortex and perirhinal cortex via reverse connections during episodic memory recall. The feedback interaction between the inferior parietal cortex and the prefrontal cortex is involved in the production of conscious experience as well as in the encoding of episodic memory. Hence one has an anatomical and functional connection between the production of conscious

experience and episodic memory.

Focal Attention and Working Memory

Prinz (2003; Attention as the mechanism of consciousness, Lecture at *TASOC* 2012 Conference) found that awareness (conscious experience) does not arise without attention and develops over a time delay. Prinz suggested this time delay may be the time necessary for attention to act. Joseph (2000) and Prinz found the inferior parietal cortex is involved in attention, perception, and working memory. Working memory also operates in the dorsolateral prefrontal cortex (Fuster, 1997, 2000, 2008; Goldman-Rakic, 1990, 1995). Working memory is the holding in mind of a number of pieces of information and its manipulation for a short period of time so that it can be utilized at a later time for goal-directed responses. Functionally, working memory is the provisional retention of perceptual information for prospective action, a type of focal attention whereby perception is reorganized and rerepresented, becoming explicit, functional, and conscious (Luck & Vogel, 1997; Todd & Marois, 2004; Vogel & Machizawa, 2004). Working memory is a cognitive process that is accompanied by consciousness (Fuster, personal communication, 2013). Working memory represents the two components (perception, focal attention) necessary for the production of conscious experience. Working memory may be formed and maintained by reentry (Fuster, 1997; 2008). Reentry refers to reciprocal interaction and occurs throughout the brain (Tonelli & Edelman, 1998). Consciousness is impaired if the reentry mechanisms of the brain are disrupted (Tonelli & Edelman, 1998). Positive feedback is a type of reentry. Positive feedback occurring in prefrontal-inferior parietal cortex connections may be a type of working memory (focal attention) whereby perception is reorganized and rerepresented, becoming explicit, functional, and conscious. The reorganization and rerepresentation of perception occurring in working memory is not entirely predictable and probably arises in a nonlinear fashion typical of complex systems like the brain (Gershenson & Heylighen, 2004). Positive feedback (and nonlinear emergence) in prefrontal-inferior parietal cortex connections therefore may be a type of focal attention (working memory) which produces conscious experience. Conscious experience is in effect arising from focal attention and perception. Any disruption in the positive feedback interaction between the prefrontal cortex and inferior parietal cortex would be tantamount to a disorder of attention (resulting in neglect). As will be seen, working memory is also involved in the encoding of episodic memory. Hence working memory appears to be the functional connection between episodic

memory and conscious experience, since working memory is involved in the formation of both conscious experience and episodic memory.

Positive Feedback, Nonlinear Emergence, Conscious Experience, Episodic Memory

Positive feedback and nonlinear emergence work in conjunction as a basic physical mechanism responsible for a vast number of natural phenomena (Scott, 1996, 1999, 2000, personal communication; Sieb, 2004, 2007, 2011, 2013). A positive feedback cycle arises in a system when part of the output of the system feeds back as an additional excitatory input into the system, producing more output, which feeds back as more input, producing more output, and so on. Positive feedback is positive loop gain around a feedback loop (Zeigler et al, 2000; Zuckerman & Jefferies, 1996). Positive feedback results in further change in the same direction. Positive feedback will increase the function of a system and the system will grow indefinitely, resulting in instability of the system (Amos & Amos, 2002; Graf, 1999; Zeigler et al, 2000; Zuckerman & Jeffery, 1996). When the loop gain is positive and above 1, there will typically be exponential growth, increasing oscillation, and divergence from equilibrium (Zeigler et al, 2000). System parameters may rapidly progress to extreme values, damage or destruction of the system may occur, or the system may latch onto a new stable state. Some positive feedback cycles produce exponential growth, but all produce unlimited growth and instability. Negative feedback results in change in the opposite direction. Negative feedback will decrease the activity of a system, act to stabilize the system, and bring it back into equilibrium. Negative feedback has a modulating influence. Positive feedback may be reduced, cancelled, or controlled by negative feedback. Negative influences therefore will inhibit or dampen the effects of positive feedback and result in a balanced equilibrium stable state of the system (Scott, 1996, 1999, 2000, personal communication; Sieb, 2004, 2007, 2011, 2013). Because many of the positive and negative influences are nonlinear (are not proportional to the output), the new stable states are said to be nonlinear emergent states.

Phenomena Arising From Positive Feedback and Nonlinear Emergence

The prototypical example of a phenomenon arising from positive feedback and nonlinear emergence is a candle flame (Scott, 1996). When a candle is lit, wax vapor burns, and heat (and light) is dissipated. Some of the dissipated heat feeds back to melt more

candle wax, producing more wax vapor, which burns, producing more heat, some of which feeds back, and so on, producing a positive feedback cycle. Nonlinear inhibitory influences (loss of heat, cross-sectional area of the candle, density of the candle wax, wind, temperature, humidity, etc.) act to inhibit or dampen the positive feedback and result in the formation of a stable equilibrium state (a balanced dissipation of heat and light, a candle flame). The candle flame is a new phenomenon (has new properties) that emerge from positive feedback and nonlinear emergence and cannot be precisely predicted in advance. The candle flame is an explicit (physical) state that can affect other physical systems and processes (it can burn fingers, ignite inflammable substances). A wave also may be described in terms of positive feedback and nonlinear emergence (Scott,1996;Sieb,2004,2007,2011,2013). When a rock is thrown into a pond, it displaces water molecules. Some adjacent water molecules move in to occupy the space previously occupied by the displaced molecules to further displace the water molecules, some of which feedback, and so on, producing a positive feedback cycle. Nonlinear inhibitory influences (weight and density of water molecules, currents, temperature, wind, obstacles, depth, other waves, etc.) act to inhibit or dampen the positive feedback resulting in the emergence of a new balanced stable state (a wave), which propagates across the water. Waves are new explicit states that can affect other physical systems and processes (boats, swimmers, other waves). A business may be described in terms of positive feedback and nonlinear emergence. An inventory of goods or services is sold. Sale of this inventory provides funds for the purchase of more inventory or services, which are sold, providing more inventory or services, and so on, producing a positive feedback cycle. Negative influences (size and type of inventory or services, number of employees, number of customers, hours of operation, damage, sickness, expenses, etc.) inhibit the positive feedback and result in a balanced equilibrium state (a specific restaurant, company, railroad, department store, particular business). Stock markets, nations, nerve impulses, cells, groups, families, political parties, and many other phenomena may be described in terms of positive feedback and nonlinear emergence.

Explicit states developed from positive feedback and nonlinear emergence have the following properties (Sieb,2004,2007,2011,2013): they are self-generated, separate and distinct, take time to form, have new properties, persist for a period of time, are explicit, can affect other physical systems and processes, are bounded, have content, have limited capacity, are variable, flexible, seamless, ineffable, transparent, serial in

production, prone to interference, unified and coherent, and project outwards. Nonlinear explicit states have the same properties as conscious experiences and episodic memories. Positive feedback and nonlinear emergence results in distinct separate identifiable states. In fact, positive feedback and nonlinear emergence is a quintessential example of discrete processing. Conscious experiences and episodic memories have all the same properties as states arising from positive feedback and nonlinear emergence. This suggests that conscious experiences and episodic memories may arise from positive feedback and nonlinear emergence. Since both arise from working memory and working memory has been described as a positive feedback-nonlinear emergent process, working memory appears to be a positive feedback-nonlinear emergence process giving rise to conscious experience and episodic memory.

Organization of Consciousness and Explicit Memory

Conscious experiences make up the content of consciousness. These conscious experiences have a particular spatiotemporal organization in consciousness at any one time. Some conscious experiences occur simultaneously, but in different locations, while other conscious experiences occur in the same locations, but at different times. Thus space and time dimensions are introduced into the organization of consciousness. Consciousness therefore appears to be organized in four dimensions (three dimensions of space, one dimension of time). A similar organization of conscious experiences in space and time occurs during episodic memory recall (some conscious experiences occur simultaneously, but in different locations; while other conscious experiences occur at the same location, but at different times). One therefore has a four-dimensional organization of consciousness at any one time and of episodic memory recall. Episodic memory therefore appears to be encoded, retained, and recalled in four dimensions. Einstein's special and general theories of relativity explain this four-dimensional organization quite well.

Special Relativity

Einstein's special theory of relativity depends on frames of reference (observational perspectives in space which may be described using coordinate systems). Special relativity is based on two postulates (Einstein, 1905): (1) the laws of physics (in their simplest form) are invariant (identical) in all inertial frames of reference (frames of reference in uniform transitory motion); and (2) the speed of light is the same for

all observers, regardless of the motion of the light source. The invariance (Lorentz invariance) of postulates (1) and (2) is captured by the Lorentz transformation, a mathematical expression utilized to transform the coordinates of one inertial frame of reference into the coordinates of another and to account for the independence of reference frame of the speed of light. The Lorentz transformation describes how measurements of space and time by different observers are related. It reflects that observers moving at different speeds may measure different distances, elapsed times, and orderings of events. The Lorentz transformation predicts relativistic interval conservation and the constancy of the speed of light. Einstein also found that all frames of reference are in inertial motion and that there is no absolute state of rest from which the motion of other inertial frames may be measured (Rindler,1777;Taylor & Wheeler, 1992).

Special relativity implies a wide range of consequences (which have been experimentally verified). These include length contraction, time dilation, relativistic mass, mass-energy equivalence ($E=mc^2$, where c is the speed of light in a vacuum), a universal speed limit (c), and relativity of simultaneity (Roberts & Schleif,2007). Combined with other laws of physics, the two postulates of special relativity predict the equivalence of mass and energy (Einstein,2001;Feynman,1998). Special relativity has replaced the notion of an absolute universal time with the notion of time that is dependent on reference frame and spatial position. Events that occur at the same time for one observer could occur at different times for another. Rather than an invariant time interval between two events, there is an invariant spacetime interval, which takes into account not only space, but time as well. Time and space cannot be defined separately from one another, but are interwoven into a single continuum (the spacetime continuum). Special relativity is restricted to flat spacetime and its geometry known as Minkowski spacetime (Minkowski,1908). Galilean relativity (the laws of motion are the same in all inertial systems) is considered an approximation of special relativity valid at low speeds. Special relativity is considered an approximation of general relativity valid in weak gravitational fields.

General Relativity

Einstein's general relativity is a geometric theory of gravitation. General relativity is based on curved spacetime and its geometry known as semi-Riemann spacetime. According to general relativity, gravity is not a force per se, as in

Newtonian physics, but is the curvature (distortion) of spacetime produced by the mass-energy contained in that spacetime (any physics text). At the core of general relativity are the Einstein Field Equations, which describe the relationship between the curvature of four-dimensional spacetime and the energy-momentum contained in that spacetime (Wald,1984; any physics text). Objects in free fall (not subject to any external forces) move along geodesics (lines in curved spacetime). A body in free fall actually moves freely along a curved path or trajectory (geodesic). This has been repeatedly demonstrated in experiments in which the instantaneous vectors (a vector is a geometric entity having magnitude and direction) calculated along the trajectory of a body in free fall vary with the trajectory. Free fall is equivalent to pure (inertial) motion within the curved geometry of spacetime (Poisson,2004).

Because general relativity (the Einstein Field Equations) is constructed using tensors (tensors express relations between vectors, scalars, or other tensors and so are dimensionless), it exhibits general covariance (its laws take on the same form in all frames of reference-Wald,1984). Hence general relativity satisfies the more basic principle of relativity (the laws of physics are the same for all observers-Guilini,2006). Locally, the spacetime of general relativity is Minkowskian and the Einstein Equivalence Principle holds (the laws of special relativity are a good approximation-Guilini,2006;Mermin,2005; Rindler,2001). A locally Lorentz invariant frame of reference that abides by the laws of special relativity can be defined at sufficiently small scales in the curved spacetime of general relativity.

Spacetime

Spacetime is any mathematical model that combines space and time into a single continuum. Mathematically, spacetime is a manifold (a description at small scale using a coordinate system). Dimensions are the independent components of a coordinate grid system used to locate points or positions in a defined space. In a Minkowski (flat spacetime) manifold and a semi-Riemann (curved spacetime) manifold, there are three dimensions of space and one dimension of time (four dimensions). Occurrences in spacetime are known as events. An event is the fundamental entity of observed physical reality represented by three coordinates of place and one coordinate of time in the spacetime continuum postulated by the theory of relativity (Merriam-Webster). Events represent the basic elements of four-dimensional spacetime. An observer chooses a convenient

metrical coordinate system when describing physical phenomena (events) occurring in spacetime. Coordinates specify where and when events occur. In spacetime, an event has a unique position at a unique time (specified by four coordinates). Spacetime may be viewed as a union of all events (like a line is a union of all its points), formally organized into a manifold. Spacetime is independent of any observer (Matolcsi,1994).

Spacetime Intervals

A line joining two events in spacetime is the shortest distance between the two events. Such lines in flat (Minkowski) spacetime are called world lines. In general relativity, the notion of a geodesic generalizes the notion of a world line to curved spacetime. A world line or geodesic between two events in spacetime is called a spacetime interval. A spacetime interval is the separation of two events in four-dimensional spacetime. Since spacetime has three dimensions of space and one dimension of time, a spacetime interval has both spatial and temporal components. Spacetime intervals are invariant (identical) in all frames of reference because of the symmetry of the laws of physics.

The unification of space and time is exemplified by selecting a metric (a measure) such that all four dimensions of spacetime are measured in units of distance (Petkov,2010). Thus an event is represented as $(x_0, x_1, x_2, x_3) = (ct, x, y, z)$ in the Lorentz Metric or as $(x_1, x_2, x_3, x_4) = (x, y, z, ict)$ in the Minkowski Metric. In three-dimensional (Euclidian) space, the separation between two objects is measured by the distance between them. In four-dimensional spacetime, the separation between two events is measured by the invariant spacetime interval between the two events. This may be formulated as follows: the spacetime interval "s" is defined as the difference between the space coordinates " Δr " of two events minus the product of "c" and the difference between the time coordinates " Δt " of the two events (in practice the square is utilized as the sign of the spacetime interval "s" is indefinite-positive, negative, or zero).

$$(\text{spacetime interval}) \quad s^2 = \Delta r^2 - c^2 \Delta t^2$$

There are three types of spacetime interval which define the spatiotemporal organization and relationships of events in spacetime (Figs.1 and 2). In a time-like spacetime interval (Fig.1), the difference in the time coordinates of two events (A and B) is greater than the difference in the space coordinates of the two events ($c^2 \Delta t^2 > \Delta r^2$). Hence the spacetime interval is

negative ($s^2 < 0$). Time-like spacetime interval separation occurs inside the light cones of Figures 1 and 2. Time-like spacetime separation creates reference frames where two events (A and B) occur at the same location in space, but are separated only by occurring at different times (they are separated by time, not by space). Time-like separation between events allows signals or information to travel between the events at less than the speed of light. Hence for an event A, there exists a set of events that can either influence or be influenced by A, by signals or information that does not need to travel faster than the speed of light. A cause or effect relationship could exist between the two events (one event could be the cause or the effect of the other event). If B causes A, B exists in the past history (in the past light cone) of A (Figs.1 and 2). If B is caused

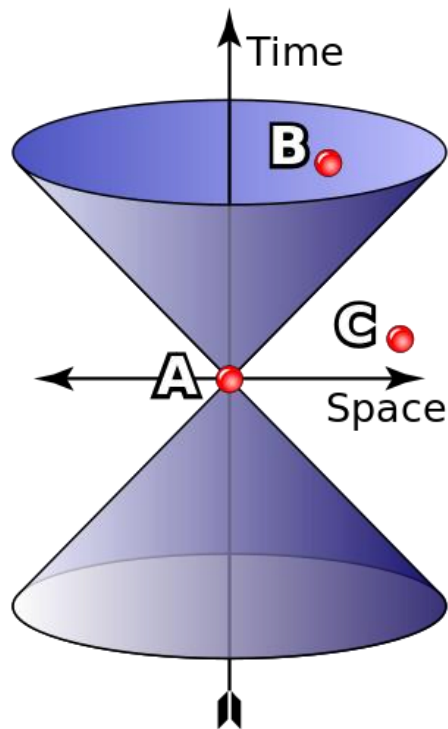


Fig. 1

by A, B exists in the future (the future light cone) of A

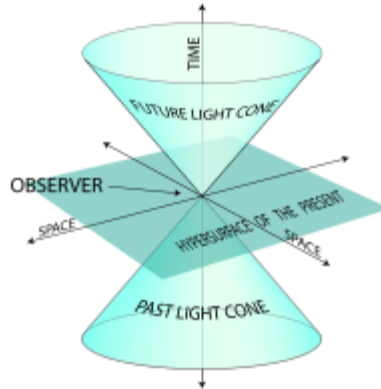


Fig. 2

(Figs.1 and 2). In a light-like spacetime interval (Figs.1 and 2), the difference in the time coordinates of two events is equal to the difference in the space coordinates of the two events ($\Delta r^2=c^2\Delta t^2$). The spacetime interval equals zero ($s^2=0$). Events following one another at light speed have light-like separation. Light-like spacetime intervals define the boundaries of the light cones of Figures 1 and 2. All the events that follow an event at light-like separations define a future light cone (Figs.1 and 2) for that event. All the events that precede an event at light-like separations define a second inverted past light cone (Fig.1 and 2) for that event. Events (A and B) occurring inside a light cone have time-like separation. Events occurring on a light cone have light-like separation (such as for a photon travelling through space). Events occurring outside a light cone have space-like separation (A and C). In a space-like spacetime interval (Fig.1), the difference in space coordinates of two events (A and C) is greater than the difference in time coordinates of the two events ($\Delta r^2>c^2\Delta t^2$). Space-like spacetime intervals are positive ($s^2>0$). Space-like spacetime separation creates reference frames in which two events (A and C) may occur simultaneously, but in different locations (they are separated only by space, not by time). There is not enough time between the two events so that one can send signals or information to the other at less than the speed of light. Hence the two events cannot influence one another (they cannot have a cause or effect relationship). Because the two events occur outside the light cone, signals or information must travel faster than the speed of light in order for one event to influence the other (this violates special relativity). A paradox of causality could exist if it was possible for a cause or effect relationship to exist between two events with space-like separation. For example, if A was the effect and C the cause, there would be a frame of reference where the effect would precede the cause. This would require faster than light signals be sent back into one's past. If A

was the cause and C the effect, signals from A would still have to travel faster than the speed of light to influence C. Therefore a cause or effect relationship cannot exist between two events with space-like separation.

Some important points should be noted from the above. Spacetime intervals are invariant (identical) in all frames of reference (for all observers), even though the observers may be travelling at different speeds or have different vantage points. Events with time-like spacetime separation are separated only by time, not by space. These events may occur at the same location, but at different times. A cause or effect relationship may exist between two events with time-like separation because signals or information may be transferred between them at less than the speed of light. Events with light-like spacetime separation are separated at light speed. Events with space-like spacetime separation are separated only by space, not by time. These events may occur simultaneously, but at different locations. These events cannot bear a cause or effect relationship to one another because there is not enough time for signals or information to be transferred between them at less than the speed of light. Spacetime intervals determine the organization and relationships of events.

Spacetime Intervals and the Organization of Consciousness and Episodic Memory

Spacetime intervals appear to determine the organization of consciousness and episodic memory. Conscious experiences make up the content of consciousness. At any one time, some conscious experiences occur simultaneously in consciousness, but in different locations. These conscious experiences may have space-like spacetime interval separation. Other conscious experiences occur at the same location in consciousness, but at different times. These conscious experiences may have time-like spacetime interval separation. Spacetime intervals therefore appear to define the organization and relationships of conscious experiences in consciousness at any one time. Consciousness therefore has a four-dimensional organization. Similarly, conscious experiences make up the content of episodic memory recall. During episodic memory recall, some conscious experiences occur simultaneously, but in different locations (space-like separation), while other conscious experiences occur at the same location, but at different times (time-like separation). Spacetime intervals therefore appear to define the organization and relationships of episodic memory recall. Episodic memory recall therefore appears to have a four-

dimensional organization.

Episodic Memory

In general, there are three main stages to memory function. First, information must be encoded or registered into memory. Second, this information must be retained in some way. Third, the stored information may be retrieved or recalled. Four types of memory appear to operate simultaneously and sequentially in the establishment of episodic memory. These are sensory memory, working memory, short term memory, and long term memory.

Sensory Memory

Sensory memory is a fast-decaying register of sensory information. It is a very brief (<1000 msec) pre-categorical high-capacity memory which occurs after stimulus offset (Sperling,1960;Dick,1974). Sensory memory is a part of the brain's memory system. It is known as iconic memory in the visual system and echoic memory in the auditory system. Sensory memory is highly colored by the sensory modality in which it occurs. This type of memory decays faster than one can report its details, so it is difficult to determine all the information that it contains.

Iconic memory provides a smooth flow of visual information to the brain which can be extracted over an extended period of time by working memory for consolidation into more stable forms. Iconic memory consists of three components (Coltheart,1980; DeLollo,1980;Loftus et al,1992). Neural persistence is the neural activity that persists in the visual system after stimulus offset. It includes activity arising in photoreceptors, ganglion cells, and simple cells. Visual persistence arises from neural persistence and is the visible phenomena that can be seen after stimulus offset (glow of a light bulb after it is turned off, path of a torch when it is moved) lasting 100-300 msec (Haber,1970;Irwin & Thomas,2008; Levick & Zack,1970;Long,1980;Nicolic et al,2009). Visible persistence is sensitive to the physical properties of the stimulus and is inversely related to stimulus duration and luminosity (Coltheart,1980). Information persistence is the non-visible information about a stimulus that persists after stimulus offset, such as spatial location and other abstract characteristics of the stimulus (Irwin & Yeomans,1986). Information persistence is proportional to stimulus duration and is the key component of iconic memory contributing to working memory (Coltheart,1980;Green,2007;Irwin & Yeomans,1986).

Information persistence could carry information about stimulus spacetime separation, such as whether stimuli occur simultaneously at different locations or whether stimuli occur at the same location but at different times (spacetime intervals), that might determine the organization of working memory.

Working Memory

Working memory is the holding in mind for a brief period of time of multiple pieces of information and its manipulation (Baddeley, 2003; Cowan, 2008; Fuster, 1997; Schacter, 2009). Working memory is not prolonged by rehearsal. Functionally, working memory is the provisional retention of perceptual information for prospective action, a type of focal attention whereby perception is reorganized and rerepresented, becoming explicit, functional, and conscious (Luck & Vogel, 1997; Schacter, 2009, 2011; Todd & Marois, 2004; Vogel & Machizawa, 2004). As already discussed, working memory is the nonlinear emergence of a number of explicit stable states (conscious experiences) from the positive feedback interaction between the inferior parietal cortex and the prefrontal cortex.

Cowan (2001) has proposed that working memory has a capacity of about four chunks in young adults (fewer in children and older adults), depending on the category (digits, letters, words, etc.) and features (short words, long words, simple words, complex words, etc.) of the chunks (Hulme et al, 1995). Chunking is the separation of information into meaningful groups called chunks so that all of the information is more easily remembered. The ideal size for a chunk is a series of three letters or numbers (like telephone numbers). Working memory enables the completion of goal-directed actions (voluntary intentional actions). It involves the holding of information over a short period of time (a delay) so that it can be utilized at a later time to perform a response (delayed response). Delayed response paradigms are therefore often used to study working memory (Fuster, 1997, 2000, 2008). Studies indicate the prefrontal cortex, inferior parietal cortex, anterior cingulate cortex, thalamus, and parts of the basal ganglia (caudate, globus pallidus) are crucial for working memory function (Ashby et al, 2005; Benton, 1991; Fuster, 1997, 2000, 2008; Goldman-Rakic, 1990, 1995; Joseph, 2000; Prinz, 2003). Goldman-Rakic (1995) showed that the dorsolateral prefrontal cortex interconnects with all these brain regions and that neuronal microcircuits within the prefrontal cortex are able to maintain information in working memory through recurrent excitatory glutamate networks of

pyramidal cells that continue to fire throughout a delay (working memory) period. These microcircuits are tuned by lateral inhibition from GABAergic interneurons (Rao et al,2000). The neuromodulatory arousal systems markedly alter prefrontal cortex working memory function; for example, either too little or too much dopamine or norepinephrine impairs prefrontal cortex network firing (Arnsten et al,2010) and working memory performance (Robbins & Arnsten,2009). A review of numerous studies shows areas of activation during working memory tasks scattered over a large part of the cortex (Smith & Jonides, 1999). There is a tendency for spatial working memory tasks to recruit more right-hemisphere areas and for verbal and object working memory tasks to recruit more left-hemisphere areas. The activation during verbal working memory tasks can be broken down into one component reflecting maintenance in the left posterior parietal cortex and a component reflecting subvocal rehearsal in the left frontal cortex (Smith et al,1998). There is an emerging consensus that most working memory tasks recruit a network of prefrontal and parietal cortical areas. As discussed previously, a prefrontal cortex-parietal cortex network is recruited during the formation of conscious experiences. Hence working memory appears to be associated with the formation of conscious experience. Honey and coworkers (2002) has shown that during a working memory task the connectivity between these areas increases. Montaghy (2006) has demonstrated that these areas are necessary for working memory and are not simply activated accidentally during working memory tasks. The prefrontal cortex has been found to be active in a variety of tasks that require executive functions (Kane & Engle,2002). This has led some researchers to argue that the role of the prefrontal cortex in working memory is in controlling attention, selecting strategies, and manipulating information, but not in maintenance. The maintenance function is attributed to more posterior areas of the brain (Curtis & D'Esposito,2003;Postle, 2006).

Research suggests a close link between working memory capacity and the ability to control the information from the environment that can be selectively enhanced or ignored (Fukuda & Vogel, 2009). The goal-directing of attention is driven by "top-down" signals from the prefrontal cortex that bias processing in posterior cortical areas (Desimone & Duncan,1995) and saliency capture by "bottom-up" control from subcortical structures and the primary sensory cortices (Yantis & Jonides,1990). The ability to override saliency capture differs greatly between individuals and this difference closely links to their working memory capacity. The greater a person's working memory

capacity, the greater their ability to resist saliency capture (Fukuda & Vogel,2009). The limited ability to override saliency capture is likely to result in the unnecessary storage of information in working memory (Fukuda & Vogel,2009), suggesting not only that having a poor working memory affects attention, but that it can also limit the capacity of working memory even further.

There is a link between working memory, attention, learning, cognitive development, cognitive function, and memory. The greater is the capacity of working memory, the better are these functions (Alloway & Alloway,2010;Andrews & Halford,2002;Berry et al,2009;Case,1985;Cowan & Alloway,2008;Kail,2007;Klingberg et al,2002;Jarrold & Bayliss,2007;Zanto & Gazzaley,2009). These studies show that working memory capacity is a better predictor of academic and occupational success than IQ.

Conscious experience and episodic memory appear to be related by working memory. They both arise from working memory and both have the same four-dimensional organization and relationships. Consciousness is also required for episodic memory recall. Working memory appears to be responsible for the basic four-dimensional organization and relationships of consciousness and episodic memory recall. As previously described, working memory is a positive feedback interaction between the inferior parietal cortex and the prefrontal cortex which produces and maintains a number of nonlinear explicit states. Working memory is the holding in mind and manipulation of a number of pieces of information for a short period of time. Hence working memory is the holding in mind and manipulation of a number of nonlinear explicit states (conscious experiences) developed from positive feedback and nonlinear emergence. Each nonlinear explicit state has a spatiotemporal location in working memory. Working memory therefore consists of a four-dimensional organization of a number of nonlinear emergent explicit stable states (conscious experiences) which is maintained (and manipulated) for a short period of time and utilized at a later time for some purpose (goal-directed action, memory). The four-dimensional organization and relationships of consciousness and episodic memory is thus developed from working memory. Working memory is a link between consciousness and episodic memory.

Short Term Memory

Thanks to the hippocampus, individuals are able to store and retain new memories and retrieve them from pieces of the original (Serino & Riva,2014). It is generally agreed that the

hippocampus plays an important role in the formation of new memories about experienced events (Eichenbaum & Cohen,1993; Squire,1992;Squire & Schacter,2002). Part of this function is hippocampal detection of novel events, places, and stimuli (VanElzakker et al,2008). Some regard the hippocampus as part of a larger medial temporal lobe memory system responsible for general declarative memory (Squire,1992). A distinction may be made between conscious *recollection*, which depends on the hippocampus, and *familiarity*, which depends on portions of the medial temporal cortex (Diana et al,2007). The encoding of information into short term memory (hours to days to weeks) appears to involve establishment of a pattern of long term potentiation (long term depression may also occur) in the hippocampus, adjacent structures (dentate gyrus, subiculum), and the cerebral cortex (occipital, temporal, parietal cortex). Long-term potentiation (LTP) is a form of neural plasticity, first known to occur in the hippocampus, which is widely believed to be one of the main neural mechanisms by which memory is stored in the brain. Severe anterograde amnesia (an inability to form new memories, to learn or remember new things) occurs with extensive hippocampal damage.

The hippocampus and LTP also appears to be involved in the retention of short term memory. LTP has been shown to occur in the hippocampus and dentate gyrus (Deadwyler et al,1988;Eccles et al,1987;Gustafsson & Wigstrom,1990;Haas & Buzsaki,1988;Lynch et al,1990;Steward et al,1988). LTP is a prolonged increase in transmission through pathways subjected to repetitive high frequency stimulation. The effect may last for days to weeks and exhibits many of the characteristics of a learning and memory mechanism. The establishment of patterns of LTP in the hippocampus and related structures is a way of encoding and retaining information for the short term. Hippocampal damage appears to disrupt the retention of short term memories. Hippocampal damage appears to affect not only the encoding and retention of new memories (anterograde amnesia), but also affects access (recall, retrieval) of memories laid down prior to the damage (retrograde amnesia) in a graded manner (the retrograde amnesia effect decreases the further back in time were recorded the memories). This retrograde effect may extend back several years prior to the damage and in some cases memories beyond this period remain unaffected. This sparing effect suggests that consolidation of memories over time involves the transfer of information out of the hippocampus to other brain areas. However, the role of the hippocampus in maintaining older memories is uncertain.

Hippocampus

There are four main histological divisions of the hippocampus: CA1, CA2, CA3, and CA4 (Wechsler,2004). The hippocampus plays an important role in the encoding and retention of short term episodic memory, the consolidation of information from short term memory to long term memory, and spatial navigation. The hippocampus receives highly processed sensory, emotional, and cognitive information from cortical association areas (temporal, parietal, and occipital), the frontal cortex, the amygdaloid nuclei, the septal nuclei, the dentate gyrus, and other structures via the entorhinal cortex (Carlson et al,1982;Flood & Coleman,1990;Goldman-Rakic,1990;Van Hoesen & Hyman,1990). The superficial layers of the entorhinal cortex provide most of the input to the hippocampus, while the deeper layers receive the most output from the hippocampus. The entorhinal cortex is located in the parahippocampal gyrus and is considered part of the hippocampal region because of its anatomical connections. The entorhinal cortex is strongly and reciprocally connected with many other parts of the cerebral cortex. In addition, the medial septal nucleus, the anterior nuclear complex and nucleus reuniens of the thalamus, the supramammillary nucleus of the hypothalamus, as well as the raphe nuclei (serotonergic) and locus coeruleus (norepinephrinergic) in the brainstem send axons to the entorhinal cortex. The main output pathway of the entorhinal cortex comes from the large stellate pyramidal cells in layer II that "perforate" the subiculum and project densely to the granule cells in the dentate gyrus, less densely to the apical dendrites of CA3, and sparsely to the apical dendrites of CA1. This "perforant path" establishes the entorhinal cortex as the main "interface" between the hippocampus and other parts of the cerebral cortex. Dentate granule cell axons (called mossy fibers) pass on the information from the entorhinal cortex to the proximal apical dendrites of CA3 pyramidal cells. Then, CA3 axons exit from the deep part of the cell body and loop up into the region where the apical dendrites are located, then extend all the way back into the deep layers of the entorhinal cortex (the Schaffer collaterals which complete the reciprocal circuit); field CA1 also sends axons back to the entorhinal cortex, but these are more sparse than the CA3 projection. Within the hippocampus, the flow of information from the entorhinal cortex is largely unidirectional, with signals propagating through a series of tightly packed cell layers, first to the dentate gyrus, then to the CA3 layer, then to the CA1 layer, then to the subiculum, and then out of the hippocampus to the entorhinal cortex, mainly due to collateralization of the CA3 axons. Each of these layers also contains complex intrinsic circuitry and extensive longitudinal connections (Amaral & Lavenex,2006). Several other connections

play important roles in hippocampal function (Amaral & Lavenex, 2006). Besides the output to the entorhinal cortex, additional output pathways go to other cortical areas including the prefrontal cortex, the lateral septal area, and the mammillary body of the hypothalamus. The hippocampus receives modulatory input from the serotonin, norepinephrine, and dopamine systems and from the nucleus reuniens of the thalamus to field CA1. A very important projection comes from the medial septal area, which sends cholinergic and GABAergic fibers to all parts of the hippocampus. The inputs from the septal area play a key role in controlling the physiological state of the hippocampus; destruction of the septal area abolishes the hippocampal theta rhythm and severely impairs certain types of memory (Winson, 1978).

The cortical region adjacent to the hippocampus is known collectively as the parahippocampus (Eichenbaum et al,2007). It includes the entorhinal cortex and the perirhinal cortex. The perirhinal cortex plays an important role in visual recognition of complex objects. There is also substantial evidence that the perirhinal cortex makes a contribution to episodic memory, which can be distinguished from the contribution of the hippocampus. It is apparent that complete amnesia occurs only when both the hippocampus and the parahippocampus are damaged (Eichenbaum et al,2007).

Various parts of the hippocampal formation are shown to be functionally and anatomically distinct. The dorsal, ventral, and intermediate regions of the hippocampal formation have varying degrees of place field neurons, have different projections, and serve different functions (Fanselow & Dong, 2009). The dorsal region serves for spatial memory, verbal memory, and learning of conceptual information (Pothuizen et al,2004). It also has more place field neurons than both the ventral and intermediate regions (Jung et al,1994). The intermediate region has overlapping characteristics with the ventral and dorsal regions (Fanselow & Dong,2009). Cenquizca and Swanson (2007) found moderate projections to two primary olfactory cortical areas and prelimbic areas of the medial prefrontal cortex. This region has the smallest number of place field neurons. The ventral region functions in fear conditioning and affective processes. Anagnostaras and coworkers (2002) showed that alterations to the ventral region reduced the amount of information sent to the amygdala by the dorsal and ventral regions, consequentially altering fear conditioning in rats.

Because of its densely packed neural layers, the hippocampus generates some of the largest EEG signals of any brain structure. The hippocampus has two major "modes" of activity named after the EEG patterns associated with them (Buzsaki, 2006). The theta mode appears during states of active, alert behavior (especially locomotion) and also during REM sleep. When cortical desynchronization (the presence of rapid irregular low amplitude EEG activity) occurs (during active searching, orientation, maintained and selective attention, initial stages of learning, discrimination responses, initial exposure to novel stimuli, in other words, during conscious processing-Joseph et al,1981), hippocampal theta appears (Buzsaki,2006;Foreman & Stevens,1987); that is, theta appears in the hippocampus whenever an animal or person is actively engaged with its environment. The EEG is dominated by regular waves at 3 to 9 Hertz, often continuing for many seconds. These reflect subthreshold membrane potentials which strongly modulate the spiking of hippocampal neurons and synchronise across the hippocampus in a travelling wave pattern (Lubenov & Siapas, 2009). This EEG pattern is known as a theta rhythm. Theta is very obvious in rabbits and rodents and also clearly present in cats and dogs. Whether theta can be seen in primates is a vexing question (Cantero et al,2003). In rats, theta is seen mainly when an animal is walking or in some other way actively interacting with its surroundings and during REM sleep (Vanderwoff,1969). The EEG is dominated by large regular waves (6 to 9 Hertz) and the main groups of neurons (pyramidal cells and granule cells) show sparse population activity, which means that in any short time interval, the great majority of cells are silent, while the small remaining fraction fire at relatively high rates, up to 50 spikes per second, for the most active of them. An active cell typically stays active for half a second to a few seconds. As the animal behaves, the active cells fall silent and new cells become active, but the overall percentage of active cells remains more or less constant. In many situations, cell activity is determined largely by the spatial location of the animal, but other behavioral variables also clearly influence it. The function of theta has not yet been convincingly explained (Buzsaki,2006). The most popular hypothesis has been to relate it to learning and memory. Theta may affect those aspects of learning and memory that are dependent upon synaptic plasticity (Huerta & Lisman,1993). It is well established that lesions of the medial septum (the central node of the theta system) cause severe disruptions of memory. However, the medial septum is more than just the controller of theta, it is also the main source of cholinergic projections to the hippocampus (Amaral & Lavenex,2006). It has

not been established that septal lesions exert their effects specifically by eliminating the theta rhythm (Kahana et al, 2001).

The large irregular activity mode appears during slow-wave sleep and also during states of waking immobility, such as resting or eating (Buzsáki et al,1990). During sleep or waking states when an animal is resting or otherwise not engaged with its surroundings, the hippocampal EEG shows a pattern of irregular slow waves, somewhat larger in amplitude than theta waves, which is occasionally interrupted by large surges called *sharp waves* (Buzsáki,1986). Sharp waves (randomly timed large deflections of the EEG signal lasting for 25-50 msec) dominate the EEG. They are frequently generated in sets, with sets containing up to 5 or more individual sharp waves and lasting up to 500 msec. The spiking activity of neurons within the hippocampus is highly correlated with sharp wave activity. Most neurons decrease their firing rate between sharp waves; however, during a sharp wave, there is a dramatic increase of firing rate in up to 10% of the hippocampal population. These events are also associated with short-lived high-frequency EEG oscillations called "ripples", with frequencies in the range of 150 to 200 Hertz in rats. Sharp waves are most frequent during sleep when they occur at an average rate of around 1 per second (in rats), but in a very irregular temporal pattern. Sharp waves are less frequent during inactive waking states and are usually smaller. Sharp waves have been observed in humans and monkeys. The two hippocampal activity modes can be seen in primates as well as rats, with the exception that it has been difficult to see robust theta rhythm in the primate hippocampus. There are, however, qualitatively similar sharp waves and state-dependent changes in neural population activity (Skaggs et al,2007).

One of the most interesting aspects of sharp waves is that they appear to be associated with memory. Wilson and McNaughton (1994) and numerous later studies reported that when hippocampal place cells have overlapping spatial firing fields (and therefore often fire in near-simultaneity), they tend to show correlated activity during sleep following the behavioral session. This enhancement of correlation, commonly known as *reactivation*, has been found to occur mainly during sharp waves (Jackson et al,2006). It has been proposed that sharp waves are reactivations of neural activity patterns that were encoded into memory during behavior driven by strengthening of synaptic connections within the hippocampus (Sutherland & McNaughton, 2000). Buzsáki (2006) and others propose that memories are stored within the hippocampus during behavior and then later transferred to the neocortex during sleep. Sharp waves are

suggested to drive Hebbian synaptic changes in the neocortical targets of hippocampal output pathways (Buzsaki,1989). Dreaming might be a manifestation of this consolidation process. Forgotten memories could also be reactivated at these times. Thus the hippocampus monitors and modulates cortical activity at various levels of cortical activation and encodes and consolidates episodic memory. The hippocampus, however, does cease to play a role in the retention of episodic memory after a certain period of time (Squire & Schacter,2002). That is, after a certain period of time, episodic memory appears to be retained independently of the hippocampus. This appears to occur because of the establishment of more stable and permanent connections in the neocortex. The period of consolidation may last up to five to seven years, as electroshock therapy produces retrograde amnesia which extends back five to seven years, but no further (Mohs,1991).

Damage to the hippocampus has detrimental effects on short term and long term episodic memory and the production of goal-directed behavior. Hippocampal damage appears to have an overall inhibitory effect on cortical activity (Gray & McNaughton,2000). Hippocampal damage may produce difficulties in inhibiting behavioral responsiveness, difficulties in inhibiting shifts in attention, perseveration, loss of habituation, impaired divergent thinking and response, impaired ability to learn and remember new information (anterograde amnesia) and to remember old information (retrograde amnesia), and the individual may be overwhelmed, hyperresponsive, distracted, and confused (Joseph,1990). Attention, learning, memory, and cognitive function are severely impaired. Bilateral destruction of the hippocampus produces severe anterograde amnesia (Ganong,1988;Joseph,1990). Iterative hippocampal discharge during induced seizures and the administration of drugs that alter normal hippocampal discharge also produce anterograde amnesia (Ganong,1988). Alcoholics who have anterograde amnesia (Korsokoff's Syndrome) often have lesions of the mammillary bodies, which are targets of the hippocampus (Ganong,1988).

Spatial Navigation, Spatial Memory

The hippocampus is involved in spatial navigation and spatial memory. Evidence suggests that the hippocampus is involved in processing and storing spatial information. Studies in animals have shown that there are neurons in the hippocampus called "place cells" which have spatial firing fields. These cells fire when the animal is in a particular location (place) in the environment, regardless of direction of travel. Most of these

neurons are at least partially also sensitive to head direction and direction of travel. Different cells fire at different spatial locations, so one can tell where an animal is in an environment by observing which neurons are firing. Place cells have been found in humans finding their way around a virtual reality town (Eckstrom et al,2003). The hippocampus may act as a neural representation of the layout of the environment (it is a cognitive map). Spatial navigation involves the ability to orient oneself in space, to follow directions, and to recognize familiar places (spatial memory). It depends on the hippocampus. An intact hippocampus has been shown to be necessary for simple spatial memory tasks, such as finding the way to a hidden goal (Morris et al,1982). A fully functional hippocampus appears to be necessary for humans to remember where they have been and where they are going. Getting lost and disorientation are common symptoms of hippocampal damage and amnesia. The hippocampi are more active when people are correctly navigating (Maguire et al,1998). The hippocampus has also been shown to be involved in finding shortcuts and new routes between familiar places (Maguire et al,2000).

Place Cells

A place cell is a type of pyramidal neuron found within the hippocampus that becomes active when an animal enters a particular location or place in the environment-the place field (Binder,2009;Fenton et al,2008;O'Keefe et al,1998). Studies have shown that many hippocampus neurons have place fields and fire bursts of action potentials when the freely moving animal passes through that particular part of the environment (Ekstrom et al,2003;Matsumara et al,1999;Rolls & Xiang,2006). A place cell has only one, or a few, place fields in a typical small laboratory environment, but more in a larger environment (Fenton et al,2008). There is no apparent topography in place fields in the hippocampus, neighboring place cells are as likely to have distant fields as neighboring ones (O'Keefe et al,1998). In a different environment, typically about half the place cells will still have place fields, but these will be for new places, unrelated to their former locations (Muller & Kubie,1987). Place cell firing is strongly correlated to sensory input and very responsive to spatial surroundings. Place cells tend to fire quickly when an animal enters a new open environment (Bures et al,1997). Place cells have proven to have the ability to suddenly change their firing pattern from one pattern to another ("re-mapping"). Although place cells do change their firing according to the external environment, they are stabilized to enable the system to resist small changes in sensory input, but

respond collectively and coherently to large changes (Jeffery, 2007).

Place cell responses are shown by pyramidal cells in the hippocampus proper and granule cells in the dentate gyrus (Moser et al,2008). Place cells constitute the majority of neurons in the hippocampus. Inhibitory interneurons, which make up most of the remaining cell population, frequently show significant place-related variations in firing rate that are much weaker than those displayed by pyramidal or granule cells. Place cells are typically almost silent when an animal is moving outside of the place field, but reach sustained rates as high as 40 Hertz when the animal is near the center. Neural activity sampled from 30 to 40 randomly chosen place cells carries enough information to allow an animal's location in an environment to be reconstructed with high confidence. The size of place fields varies in a gradient along the length of the hippocampus, with cells at the dorsal end showing the smallest fields, cells near the center showing larger fields, and cells at the ventral tip fields that cover the entire environment (Moser et al,2008). In some cases, the firing rate depends not only on place, but also on the direction the animal is moving, the destination toward which it is traveling, and other task-related variables (Smith & Mizumori,2006).

O'Keefe and Dostrovsky first found the existence of place cells in the hippocampus in 1971. They later demonstrated that place cells would fire whenever a rat was within a certain place in the environment (Moser et al,2008). O'Keefe (1978) found that place cells fire more rapidly when rats ran past places in the environment, when a new item was added to the environment, or when an item that is usually there is not present. This was one of the first indicators that place cells were related to spatial orientation. It might also be indicative of a temporal orientation (the presence of an item in the same location, but at different times). It was also discovered that place cells fired in different areas of the hippocampus depending on where the rat went and this whole firing network made up the rat's environment (O'Keefe 1976,Wilson & McNaughton,1993). As environments changed, the same place cells would fire, but the relationship and dynamic between firing fields would change (O'Keefe & Conway 1978). Therefore place cells are thought to give humans and animals a guide to the environment they are navigating and their position in that environment. As humans and animals navigate large environments and then arrive at a particular location, there is a notable increase in the place cell firing rate once that specific location has been reached (Eichenbaum et al,1999). Place cells fire in different, often

widespread, hippocampal locations at the same time (O'Keefe, 1999). This also might indicate that place cells signal temporal orientation. Place cells that fire simultaneously, but in different locations in the hippocampus, and place cells that fire at the same locations in the hippocampus, but at different times, may add a temporal dimension to hippocampal function. Hence place cells may be encoding, not just a three-dimensional cognitive map of the environment, but a four-dimensional cognitive map of the environment.

In an open field environment, firing fields of place cells prove to be similar even when a rat travels in different directions (O'Keefe,1999). When limitations are placed in the aforementioned environment, firing fields prove to be directional and fire in one direction, but not in another (O'Keefe,1999). There are both simple place cells with purely location correlates and also complex place cells that increase their firing rate when an animal encounters a particular object or experience (O'Keefe,1999). Others fire when expectations in a particular location are not met or when novelty is encountered along the path.

The existence of place cells within the hippocampus demonstrates the important role it plays in spatiotemporal adaptation and awareness. There have been recorded increases in firing patterns in open environments and spatial learning and awareness impairments after damage to the hippocampus and the place cells within (Binder,2009). Place fields are considered to be allocentric rather than egocentric, meaning that they are defined with respect to the outside world rather than the body. By orientation based on the environment, rather than the individual, place fields can work effectively as neural maps of the environment (Jeffery et al,2003). If this cognitive map is in four dimensions (a neural representation of the four-dimensional layout of the environment) then the hippocampus could participate in the four-dimensional organization of awareness (consciousness) and episodic memory. Several lines of evidence support this hypothesis. It is a frequent observation, that without a fully functional hippocampus, humans may not remember where they have been or how to get where they are going (getting lost is one of the most common symptoms of amnesia-Chui et al,2004). Studies have shown that an intact hippocampus is required for initial learning and retention in some spatial memory tasks, in particular, ones that require finding the way to a hidden goal (Clarke et al,2005;Morris et al,1982;Sutherland et al,1982;Sutherland et al,2001). The cognitive map hypothesis has been further advanced by recent discoveries of head direction cells, grid cells, and boundary cells in several parts

of the brain that are strongly connected to the hippocampus (Moser et al,2008;Solstad et al,2008). People have more active hippocampi when correctly navigating, as tested in computer-simulated "virtual" navigation tasks (Maguire et al,1998). Also, there is evidence that the hippocampus plays a role in finding shortcuts and new routes between familiar places. A study by Maguire and coworkers (2000) showed that part of the hippocampus is larger in taxi drivers than in the general public and that more experienced drivers have bigger hippocampi. The study found a positive correlation between the length of time an individual had spent as a taxi driver and the volume of the right hippocampus.

Place cells therefore may act collectively as a four-dimensional cognitive map of the environment. Place cells work with other types of neurons in the hippocampus and surrounding regions to perform this kind of processing (Muir & Bilkey,2001). Head direction neurons increase their firing rates above baseline levels only when the animal's head points in a specific direction. When stimulated these neurons fire at a steady rate (they do not show adaptation), but decrease back to their baseline rates, as the animal's head turns away from the preferred direction (usually about 45° away from this direction-Taube,2007). These cells are found in many brain areas, including the post-subiculum, retrosplenial cortex, the thalamus (anterior and the lateral dorsal thalamic nuclei), lateral mammillary nucleus, dorsal tegmental nucleus, striatum, and entorhinal cortex (Sargolini et al,2006). This system is related to the place cell system, which is mostly orientation-invariant and location-specific, while head direction cells are mostly orientation-specific and location-invariant. However, head direction cells do not require a functional hippocampus to show their head direction specificity.

Place cells are a part of a complex circuit that informs awareness and memory (Smith & Mizumori,2006). Place cell circuits have important implications for memory as they provide a context for such memory (Smith & Mizumori,2006). Like many other parts of the brain, place cell circuits are dynamic. They are constantly adjusting and remapping to suit the current environment. Place fields are roughly analogous to the receptive fields of sensory neurons in that firing corresponds to a representation of sensory information in the environment (Ryan,2013). Place cells respond to complex stimuli rather than simple individual sensory cues (Jeffery et al,2003;Moser et al, 2008). Sensory information is processed in various cortical structures upstream of the hippocampus before actually reaching the structure, so that the information received by place cells

is a compilation of different stimuli (Jeffery et al,2003). Sensory information received by place cells can be metric or contextual (Jeffery,2007). Metric corresponds to where place cells should fire while contextual corresponds to whether or not a place field should fire in a certain environment. Metric sensory information may be any kind of input that might indicate a separation between two points (such as separation in spacetime). Metric signals can be either linear or directional. Directional inputs provide information about the orientation of a place field, whereas linear inputs essentially form a representational grid. The entorhinal cortex is the main input to the hippocampus. The entorhinal cortex contains head direction cells and grid cells. It seems probable that it is the head direction cell input that directs the orientation of place fields in the hippocampus and the grid cells that direct the grid-like representation of place fields in the hippocampus. Contextual cues allow established place fields to adapt to minor changes in the environment, such as a change in object color, shape, or location. Metric and contextual inputs are processed together in the entorhinal cortex before reaching the hippocampal place cells. Visual and olfactory inputs are examples of sensory inputs that are utilized by place cells. These types of sensory cues can include both metric and contextual information (Jeffery,2007). Spatial cues such as geometric boundaries or orienting landmarks are also important metric input. So-called boundary or border cells are found in the entorhinal cortex which appears to provide such input to place cells. Place cells rely on set distal cues rather than cues in the immediate proximal environment (Jeffery,2007). Movement can also be an important metric cue. The ability of place cells to incorporate new movement information is called **path integration** (Moser et al,2008). Path integration is largely aided by grid cells in the entorhinal cortex that relay information to place cells in the hippocampus. As will be seen, grid cells may establish a four-dimensional regular grid representation of spacetime in the hippocampus, so that during movement place cells can fire according to a reference grid of their external environment (Jeffery,2007). Visual inputs can supply important contextual information. A change in color of a specific object can affect whether or not a place field fires in a particular environment (Jeffery,2007). Although place cells primarily rely on visual input, some studies suggest that olfactory input may also play a role in generating and recalling place fields and orientation during movement (Save et al,2000; Zhang & Manahan-Vaughn,2013).

The hippocampus plays an essential role in episodic memory (Rolls,2013). One important aspect of episodic memory is the

context in which the event occurred (Smith & Mizumori,2006). Hippocampal place cells have been shown to exhibit stable firing patterns even when cues from a location are removed. Additionally, specific place fields begin firing when exposed to signals or a subset of signals from a previous location (Nakazawa et al,2004). Place cells therefore appear to prime memory by differentiating the context (Smith & Mizumori,2006). Hence place cells may complete memory patterns (Rolls,2013). Furthermore, place cells can maintain representation of one location while recalling the neural map of a separate location, effectively differentiating between present experience and past experience (Smith & Mizumori,2006). Place cells therefore demonstrate both **pattern completion** and **pattern separation** (Mozer et al,2008;Rolls,2013). Place cells often exhibit **reactivation** outside their place fields. This reactivation has a much faster time scale than the actual experience and it occurs mostly in the same order in which it was originally experienced, or, more rarely, in reverse. **Replay** is believed to have a functional role in memory retrieval and memory consolidation. It was also shown that the same sequence of activity may occur before the actual experience. This phenomenon, termed **preplay**, may have a role in prediction and learning.

Grid Cells

Grid cells were discovered by Moser and coworkers (2005) in the entorhinal cortex. Grid cells have multiple firing fields, with regular spacing, which tessellate the environment in a hexagonal pattern. The arrangement of the firing fields of grid cells all at equal distances from their neighbors led to a hypothesis that these cells encode a cognitive representation of Euclidian space (Hafting et al,2005). What makes grid cells especially interesting is that the regularity in grid spacing does not derive from any regularity in the environment or in the sensory input available. Grid cells appear to encode a type of abstract structure inside the brain which is imposed on the environment with no regard for the sensory features of the environment.

Unique properties of grid cells include the following (Hafting et al,2005):

1. Grid cells have firing fields dispersed over the entire environment (place fields are restricted to certain specific regions of the environment),
2. The firing fields of grid cells are organized into a hexagonal lattice,

3. Firing fields of grid cells are generally equally spaced apart such that the distance from one firing field to all six adjacent firing fields is approximately the same (though when an environment is resized, the field spacing may shrink or expand differently in different directions-Barry et al,2007),
4. Firing fields of grid cells are equally positioned such that the six neighboring fields are located at approximately 60 degree increments.

Grid cells at similar dorsal-to-ventral entorhinal cortex levels had similar grid spacing and grid orientation, but the phase of the grid (the offset of the grid vertices relative to the x and y axes) appeared to be randomly distributed between cells (Hafting et al,2005).

Grid cells fire when a freely moving animal traverses a set of small regions which are roughly equal in size and arranged in a periodic triangular array that covers the entire available environment (Hafting et al,2005). The grid cell periodic firing pattern was anchored to external landmarks, was expressed independently of the configuration of landmarks, was expressed in darkness as well as in the presence of visible landmarks, and occurred independently of changes in the animal's speed and direction. Cells with this firing pattern have been found in all layers of the dorsocaudal medial entorhinal cortex, but cells in different layers tend to differ in other respects. Layer II contains the largest density of pure grid cells, in that they fire equally regardless of the direction in which an animal traverses a grid location. Grid cells from deeper layers are intermingled with conjunctive cells and head direction cells (in layers III, V, and VI there are cells with a grid-like pattern that fire only when the animal is facing a particular direction-Sargolini et al,2006). Grid cells that lie next to one another usually show the same grid spacing and orientation, but their grid vertices are displaced from one another by apparently random offsets. Cells recorded from a distance from one another frequently show different grid spacing. Cells that are located more ventrally (that is, farther from the dorsal border of the entorhinal cortex) generally have larger firing fields at each grid vertex and correspondingly greater spacing between the grid vertices (Hafting et al,2005). Grid cell activity does not require visual input, since grid patterns remain unchanged when all the lights in an environment are turned off. When visual cues are present, however, they exert strong control over the alignment of the grids (rotating a cue card on the wall of a cylinder causes grid patterns to rotate by the same amount). Grid patterns appear on the first entrance of

an animal into a novel environment and usually remain stable thereafter. When an animal is moved into a completely different environment, grid cells maintain their grid spacing and the grids of neighboring cells maintain their relative offsets. The interactions of grid cells with place cells are interesting. When a rat is moved to a different environment, the activity patterns of hippocampal place cells usually show "*complete remapping*" – that is, the pattern of place fields reorganizes in a way that bears no detectable resemblance to the pattern in the original environment (Muller and Kubie,1987). If the features of an environment are altered less radically, however, the place field pattern may show a lesser degree of change, referred to as "*rate remapping*", in which many cells alter their firing rates, but the majority of cells retain place fields in the same locations as before. Fyhn and coworkers (2007) examined this phenomenon using simultaneous recordings of hippocampal and entorhinal cells and found that in situations where the hippocampus shows rate remapping, grid cells show unaltered firing patterns, whereas when the hippocampus shows complete remapping, grid cell firing patterns show unpredictable shifts and rotations.

Neural activity in nearly every part of the hippocampal system is modulated by the theta rhythm. The entorhinal cortex is no exception. Like the hippocampus, it receives cholinergic and GABAergic input from the medial septal area, the central controller of theta. Grid cells, like hippocampal place cells, show strong theta modulation (Hafting et al,2005). Grid cells from layer II of the medial entorhinal cortex also resemble hippocampal place cells in that they show phase precession—that is, their spike activity advances from late to early phases of the theta cycle as an animal passes through a grid vertex. Most grid cells from layer III do not show precession, but their spike activity is largely confined to half of the theta cycle. The grid cell phase precession is not derived from the hippocampus because it continues to appear in animals whose hippocampus has been inactivated by an agonist of GABA (Hafting et al,2008).

Boundary Cells

Boundary cells (border cells, boundary vector cells) are neurons found in the hippocampal formation that respond to the presence of an environmental boundary at a particular distance and direction from an animal. The firing fields of place cells, which characteristically respond only in a circumscribed area of an animal's environment, tended to fire in corresponding locations when the shape and size of the environment was altered (Burgess et al,2000;Hartley et al,2000;O'Keefe & Burgess,1996).

Boundary cells relied on inputs sensitive to the geometry of the environment (environmental boundaries at particular distances and allocentric directions) to determine where a given place cell would fire in environments of different shapes and sizes. Cells were identified with these characteristics in the subiculum (Barry et al,2006;Lever et al,2009), entorhinal cortex (Savelli et al,2008;Solstad et al,2008), and pre- and para-subiculum (Boccaro et al,2010). In medial entorhinal cortex border/boundary cells comprise about 10% of the local population, being intermingled with grid cells and head direction cells.

Long Term Potentiation (LTP)

Since the time of Ramon y Cajal (1894), scientists have speculated that the brain stores memory by altering the strength of connections between neurons that are simultaneously active. This idea was formalized by Donald Hebb in 1948, but for many years thereafter attempts to find a brain mechanism for such changes failed. In 1973, Bliss and Lømo described a phenomenon in the rabbit hippocampus that appeared to meet Hebb's specifications: a change in synaptic responsiveness induced by brief strong activation and lasting for hours to days or longer. This phenomenon was referred to as long term potentiation (LTP). As a candidate mechanism for memory, LTP has since been studied intensively.

The hippocampus is particularly favorable for studying LTP because of its densely packed and sharply defined layers of neurons, but similar types of activity-dependent synaptic change have been observed in many other brain areas (Cooke & Bliss, 2006). The best-studied form of LTP occurs at synapses that terminate on dendritic spines and use the neurotransmitter glutamate. Several of the major pathways within the hippocampus fit this description and exhibit LTP (Malenka & Bear,2004). The synaptic changes in LTP depend on a special type of glutamate receptor, the NMDA receptor, which has the special property of allowing calcium to enter the postsynaptic spine only when presynaptic activation and postsynaptic depolarization occur at the same time (Nakazawa et al,2004). LTP appears to occur because of increased Ca⁺⁺ release in the synapses of active pathways. Drugs that interfere with NMDA receptors block LTP and have major effects on some types of memory, especially spatial memory. Transgenic mice, which have a disabled LTP mechanism, also generally show severe memory deficits (Nakazawa et al,2004).

Activity Driven Synaptic Plasticity

Activity driven changes occur in the synapses between neurons which influence their further activity. This is known as activity driven synaptic plasticity. These changes may be inhibitory or excitatory. Learning and memory are hypothesized to occur via activity driven changes in the connections between neurons. Certain mechanisms normally operate at the neural synapse level to regulate firing according to the average level of activation. A mechanism that normally operates at the neural synapse level to regulate postsynaptic firing according to the average level of synaptic activity is known as synaptic (spike) timing dependent plasticity (STDP). STDP depends on the temporal occurrence of presynaptic and postsynaptic spikes. When one neuron repeatedly fires after another neuron fires, changes occur in the connections between the two neurons which facilitate further such firing. The firing of the two neurons is said to be correlated. The firing of the postsynaptic neuron is in effect regulated by the firing of the presynaptic neuron. This regulation consists of changes in the connections between the two neurons so that the connections are either strengthened or weakened. A synapse is strengthened if the firing of one neuron is repeatedly followed by the firing of the other neuron. A synapse is weakened if a neuron repeatedly fails to fire the other neuron. STDP refers to the observation that the precise timing of presynaptic and postsynaptic spikes significantly affects the magnitude and sign of synaptic response. STDP follows Donald Hebb's famous postulate for neural learning: "two neurons that fire together, wire together". Hebb's postulate may also be interpreted in another way: "if presynaptic activity repeatedly produces postsynaptic activity, then changes occur in the synapses that facilitate further postsynaptic activation by the presynaptic activation." Hence STDP is also known as Hebbian plasticity. Hebb's postulate was later extended by others so that when the presynaptic input failed to produce postsynaptic output, then the synapses were depressed. In the archetypical form of STDP, a neural connection is strengthened if the presynaptic neuron fires a few milliseconds before the postsynaptic neuron fires and weakened if the reverse temporal situation occurs, the postsynaptic neuron fires before the presynaptic neuron. The time windows for the production of potentiation and depression in this model of STDP are very different with the time window for the production of depression (up to negative 100 msec) being much broader than the time window for potentiation (positive 1-10 msec). If the synaptic connection is strengthened (STDP is called LTP). If the synaptic connection is weakened (STDP is called long term depression-LTD). STDP may be considered a type of learning and memory.

STDP provides a powerful mechanism for the modification of neural circuits. It has been implicated in cortical map development, the sharpening of sensory receptive fields, working memory, associative learning, and the stabilization of neural activity (Watt & Desai,2010). However, evidence suggests that the spike timing case for the production of STDP is an oversimplification (Shouval et al,2010;Watt & Desai,2010). STDP does not develop in a simple graded additive (linear) fashion, as would occur if it arose simply from the incremental summed effects of individual spike pairs. A simple spike timing rule does not explain many of the nonlinearities that occur in the development of activity driven synaptic plasticity (Shouval et al,2010;Watt & Desai,2010). Many forms of STDP occur in many different synapse types. Also, if the presynaptic input and/or the postsynaptic output consist of spike trains (more than one spike), then the changes that occur in the synapses are much more complex because of nonlinear interactions among the multiple spikes (Froemke et al,2010). In the particular case of high frequency input, LTP occurs regardless of the temporal order of the firings. Hence temporal order is not the most important determinant of STDP (Buchanan & Mellor,2010;Shouval et al,2010). Nonlinearities arise in the production of activity driven synaptic plasticity as a result of stimulation frequency, total number of presynaptic and postsynaptic spikes, the history of spike activity, and the location and spatial pattern of activity on and across neurons. STDP arises in an all or none manner over minutes. It does not arise in a graded incremental manner. The induction of synaptic plasticity involves a number of receptor-generated second messengers (like calcium) and the kinases, phosphatases, and other downstream targets they activate (Shouval et al,2010). All these molecular factors are ignored in a simple plasticity or learning rule involving the temporal order of spike pairs. A study of the cellular processes involved in synaptic plasticity provides a better rule for synaptic plasticity and learning by accounting for much of the nonlinearity that arises in the development of such plasticity. Calcium accounts for much of the complexity of the induction of a number of types of synaptic plasticity (Shouval et al,2010). The critical trigger for STDP is actually the influx of Ca⁺⁺ through NMDA receptors in postsynaptic membranes where the peak local postsynaptic Ca⁺⁺ concentration achieved is crucial in determining CAMKII and PPI activation and consequently the direction and magnitude of STDP (Buchanan & Mellor,2010). It is the amount of postsynaptic depolarization that is achieved at a synapse that determines the magnitude of the Ca⁺⁺ influx. Postsynaptic depolarization is responsible for

removing the Mg^{++} block from NMDA receptors and allowing the influx of Ca^{++} . Hence the greater the postsynaptic depolarization, the greater the influx of Ca^{++} . The size of the local increase in Ca^{++} concentration determines the magnitude and sign of STDP. The amount of postsynaptic depolarization achieved depends on the EPSP (excitatory presynaptic potential) amplitude, the dendritic membrane potential and excitability, the presence of inhibitory synaptic transmission, action potential back-propagation, and the frequency of stimulation (Buchanan & Mellor, 2010). If the total postsynaptic depolarization is below a certain threshold, then LTD occurs and the synapse is weakened (the postsynaptic neuron fires less strongly to the same presynaptic stimulation or it takes stronger presynaptic stimulation to fire the postsynaptic neuron). In other words, the connection weight is decreased. If the postsynaptic depolarization is above the threshold, then LTP occurs and the synapse is strengthened (the postsynaptic neuron fires more strongly to the same presynaptic input or it takes less presynaptic stimulation to fire the postsynaptic neuron). The connection weight is increased. Hence LTP and LTD are determined by the amount of postsynaptic depolarization achieved and the calcium dynamics at synapses. It is a certain threshold of postsynaptic depolarization which determines the switch over point from LTD to LTP. One therefore has the potential to have a sliding threshold of postsynaptic depolarization controlling the production of LTD or LTP. This is very important in controlling and stabilizing synaptic activity and maintaining synaptic activity at an optimal level. The threshold may be changed (regulated) by a mechanism which increases or decreases the overall excitability of the neurons involved. This mechanism is sensitive to the activity level across synapses and is very important in maintaining the stability and function of synapses when the activity levels become high or low or fluctuate. Thus, if the activity level across a synapse is increased, then an increase in the threshold (by decreasing the excitability of the presynaptic and/or postsynaptic neuron) determining the production of LTD or LTP would lead to a dampening and stabilization of the postsynaptic firing. Conversely, if the activity level across a synapse is decreased, then a decrease in the threshold (by increasing the excitability of the presynaptic and/or postsynaptic neuron) for the production of LTD or LTP would lead to an increase and stabilization of postsynaptic firing. If the excitability of a neuron was determined by the activity level (which it seems to be), then it is the activity level which controls the sliding threshold for producing LTD or LTP. Hence the activity level regulates the output. How the excitability of neurons is

controlled by their activity level will be discussed in the next section (homeostatic intrinsic plasticity).

Homeostatic Synaptic Regulation

Runaway potentiation may occur in the hippocampus from high frequency input, leading to the destabilization of neuron and neural network activity and the loss of effective information transfer and function (Watt & Desai, 2010). Other presynaptic inputs to postsynaptic neurons, which were not originally correlated with the postsynaptic firing, will also become correlated with the postsynaptic firing and LTP will occur in these connections as well. Consequently, the runaway potentiation will spread from neuron to neuron and throughout the neural network, leading to ever increasing excitation, destabilization of neural network activity, a loss of effective information transfer and function, and pathology (like in some seizures). Since such a situation does not normally occur in the brain, some mechanisms must operate to prevent such instability and pathology from occurring. In order to maintain the stability and functionality of neurons and neural circuits in the face of high frequency stimulation (or fluctuating activation), changes in synaptic strength must be regulated and coordinated across multiple synapses and with other neuronal properties. This is known as homeostatic synaptic regulation. Homeostatic synaptic regulation helps balance high and low activity levels of a neuron or neural network in order to achieve balanced and stable functionality of the neuron or neural network. This is necessary for the neuron or neural network to function optimally.

Homeostatic synaptic regulatory mechanisms prevent runaway potentiation, maintain the optimal dynamic functional range during periods of high or low activity levels and during periods of intense synaptogenesis and neural growth, and face the different stability issues arising during different developmental stages. In complicated neural circuits, homeostatic synaptic regulation encompasses different processes acting on different timescales and in different ways. There are homeostatic synaptic mechanisms that regulate a neuron's excitability, synaptic drive (input), or spiking output. STDP does not work alone. Homeostatic forms of neuronal plasticity complement and work in conjunction with STDP and forms of developmental plasticity to constrain synaptic strength and/or neuronal properties. Homeostatic plasticity mechanisms control the total synaptic strength of a neuron, modulate the intrinsic excitability of a neuron as a function of its average activity,

and control the ability of synapses to undergo Hebbian modification according to their history of use (Watt & Desai, 2010). Homeostatic plasticity mechanisms serve to regulate a neuron's output to keep it relatively stable and at an optimal level. In other words, a neuron's activity is kept in the optimal dynamic range, so that the neuron can continue to transfer information and function in an effective manner. Major forms of homeostatic synaptic plasticity that function in this manner are synaptic scaling, homeostatic intrinsic plasticity, metaplasticity, and stability mechanisms intrinsic to STDP (Watt & Desai, 2010).

Synaptic Scaling

Synaptic scaling directly regulates the synaptic strength of neurons to promote cellular stability. Synaptic scaling is bidirectional. The synaptic strength of neurons is scaled down if general activity levels are increased and scaled up if general activity levels are decreased. This tends to keep the synaptic strength and activity of neurons within the optimal dynamic functional range. Synaptic scaling occurs gradually over hours and days. It appears to occur globally over all of a neuron's synapses, but a local type of synaptic scaling has also been described (Watt & Desai, 2010). This is in contrast to STDP which occurs in only a fraction of a neuron's synapses (those that are active). Synaptic scaling also occurs so that differences in the relative strengths of various inputs of a neuron are maintained. This is important for learning and memory, as these are thought to be encoded as different synaptic strengths of neurons. The firing rate of a neuron appears to be an important determinant of synaptic scaling. Studies indicate that at the neuronal level the input that a neuron receives is titrated to keep its output stable and within an optimal range (Watt & Desai, 2010). The synaptic input to a neuron was scaled up when its firing rate was reduced to bring the firing rate of the neuron back to optimal control levels. The synaptic input to a neuron was scaled down when its firing rate was increased to bring the firing rate of the neuron back to optimal levels. In synaptic scaling, changes in postsynaptic activity are precisely balanced with presynaptic changes in release dynamics. Synaptic scaling may involve presynaptic and/or postsynaptic changes and depends on calcium dynamics and a variety of soluble second messengers (BDNF-brain derived neurotrophic factor, calmodulin activated kinases, etc.), maybe the same molecules as are involved in producing STDP (Watt & Desai, 2010). Synaptic scaling may involve changes in both AMPA and NMDA currents (Watt & Desai, 2010). Since both synaptic scaling and STDP result from

changes in Ca^{++} dynamics and the same second messengers, the two forms of plasticity may be coordinated and complement each other. The changes for synaptic scaling and STDP occur at different time scales, however. Synaptic scaling is much slower than STDP.

Homeostatic Intrinsic Plasticity

A neuron's intrinsic electrical properties arise largely as a result of the expression of various voltage and calcium dependent ion channels (Watt & Desai,2010). The expression of these channels at any one time is very complex, varies throughout life, and is under the influence of the activity level. Changes in the intrinsic properties of a neuron result in an overall shift in cellular excitability. This is known as homeostatic intrinsic plasticity. This plasticity may help neurons and neural circuits maintain appropriate levels of electrical activity under changing conditions of input. Thus the gain and/or threshold (excitability) of individual neurons for firing may be adjusted or matched to the average input received. A neuron's output (firing rate) therefore has a relation to its input. If the average input is too low, the neuron will hardly ever fire, because of the spike threshold. If the average input is too high, the neuron's firing will saturate, because there is a physical limit to how fast a neuron can fire. Between these two extremes is the sensitive region in which the neuron's output really does reflect its input. Thus there is a robust strategy for maintaining neuronal firing rate stability. When there are large or long-lasting fluctuations in average input, changes occur in the intrinsic properties (excitability) of the neurons, so that the sensitive region of the neurons' firing corresponds to the distribution of inputs received. The dynamic range of a neuron's firing is therefore preserved. In other words, neurons respond to low or high activity conditions by becoming more or less sensitive to whatever input they receive. Evidence for such a mechanism has been found in the neocortex, hippocampus, and other parts of the brain (Watt & Desai,2010). As for synaptic scaling, the signal for homeostatic intrinsic plasticity seems to be calcium influx due to depolarization and spike firing (Watt & Desai,2010). Under physiological conditions, intracellular calcium levels track average firing rates quite well. Thus one has a robust self-regulatory activity driven signaling control of the firing of individual neurons and of large neural networks. One also has the coordination of homeostatic intrinsic plasticity, STDP, and other homeostatic plasticity mechanisms, as all depend on calcium levels to some extent. Other extracellular signals may

also play a role in homeostatic intrinsic plasticity, like in synaptic scaling. The relationship of homeostatic intrinsic plasticity and synaptic scaling is unclear. These two forms of homeostatic plasticity may act together in parallel, singly at different stages of development, or synergistically. Neither appears to be sufficient alone (Watt & Desai,2010). It appears like homeostatic intrinsic plasticity affects STDP. When the average activity of a neuron is low, an increase in intrinsic excitability (a decrease in threshold) would make the subsequent production of synaptic potentiation more likely. If the average activity of a neuron is high, a decrease in intrinsic excitability (an increase in threshold) would make the subsequent production of synaptic potentiation less likely and the production of synaptic depression more likely. This plasticity of plasticity is known as metaplasticity and is a type of homeostatic adaptation.

History

From a network point of view, the most stable type of homeostatic regulation may be embedded in the rules of Hebbian plasticity (STDP). One way of doing this is to make the capacity of synapses to undergo Hebbian plasticity depend on their history of activity (their history of use). This is a form of metaplasticity. LTP occurs if the postsynaptic depolarization is above a certain threshold, while LTD occurs if the postsynaptic depolarization is below the threshold. By moving the threshold for producing LTD and LTP as a slow function of the average activity level, the capacity for undergoing Hebbian plasticity can be varied over time. In other words, the capacity of synapses to undergo Hebbian plasticity may be varied according to the history of activity level. One consequently has a sliding threshold controlling neural firing which is dependent on the history of use of the synapses. This history effect stabilizes synaptic dynamics. Many experiments have demonstrated the existence of a threshold that moves based on prior activity (Watt & Desai,2010). This sliding of the threshold has been shown to be a cell wide property and not restricted to specific synapses. The cause of this shift may be activity driven changes in NMDA receptor subunit composition, synaptic scaling of NMDA conductance, and intrinsic homeostatic plasticity (Watt and Desai,2010). STDP therefore is tempered by homeostatic synaptic plasticity mechanisms which naturally change synaptic weights so that neurons can continue to effectively transfer information. Homeostatic plasticity mechanisms stabilize synapses. Homeostatic regulation may encompass regulating and stabilizing the firing of individual

neurons or of large neural networks, preserving the uniform distribution of synaptic weights across neurons and neural networks, and ensuring that the dynamic range of response properties matches that of inputs.

Short Term Episodic Memory

Working memory appears to access the hippocampus via the entorhinal cortex (perforant path). A reverberatory circuit of activation has been shown to be set-up between the entorhinal cortex and the hippocampus during conscious processing (Deadwyler et al,1988). Such a circuit could provide prolonged repetitive high frequency stimulation adept at producing LTP in place cell assemblies of the hippocampus. An allocentric representation of the environment appears to be encoded and stored in the hippocampus (Ekstrom et al,2003;O'Keefe & Dostrovsky,1971;O'Keefe & Nadel,1978;Ono et al,1993;Serino & Riva,2014). Neurons in the CA3 region of the hippocampus, receiving inputs from the entorhinal cortex, form an *allocentric view-point dependent representation*; whereas neurons in the CA1 region of the hippocampus, receiving inputs from CA3 via Schaffer collaterals, rapidly encode an *allocentric view-point independent representation* (Robertson et al,1998;Rolls,2007). It is possible to distinguish between the allocentric representation formed by CA3 and the allocentric representation formed by CA1 (Behrendt,2013). Hippocampal place cells play a crucial role in the establishment and maintenance of both representations (Serino & Riva,2014). The encoding of activity of both the CA3 and CA1 regions in sync is necessary for the encoding of coherent short term episodic memory. Hippocampal place cells play a critical role in retrieving a coherent episodic memory because of the reciprocal connectivity between the hippocampus and neocortical regions. When prompted by a retrieval cue, the full episodic memory can be retrieved through the process of pattern completion (Burgess et al,2001;Byrne et al,2007). Episodic recall (including the simulation of future or imaginary events) may be traceable to retrieval cues (encoded in neocortical areas and introduced to the hippocampus via the entorhinal cortex) inducing the reinstatement of neuronal assemblies in CA3 and CA1 (Serino & Riva,2014). Serino and Riva (2014) suggest that for effective episodic retrieval, it is crucial that the allocentric view-point independent representation in CA1 be synced with the allocentric view-point dependent representation in CA3. In Alzheimer's disease a break in the "mental frame syncing" between these two allocentric representations may occur, caused by damage to the hippocampus,

and may contribute significantly to the early impairment of episodic memory (Serino & Riva,2014).

Long Term Memory

The storage of episodic memories for a long period of time (long term memory) involves the establishment of more stable and permanent neuronal connections in pathways previously subjected to LTP. This involves additional protein synthesis and structural change (like phosphorylation of proteins). This probably occurs most prominently in the cerebral cortex (parietal, temporal, and occipital cortex), where long term episodic memories appear to be stored. Patients with lesions in the parietal and occipital cortex may have markedly reduced memory spans, but intact learning abilities (Mohs,1991). The hippocampus may be involved in changing neuronal connections for three months or more after the initial learning. It may take years (sometimes 5-7 years) for long term episodic memories to be fully consolidated (Mohs,1991). The hippocampus appears to be responsible for the consolidation of short term episodic memory into long term episodic memory. Hence the hippocampus is necessary for not only the formation of new memories, but also for long term retention of those memories. In the absence of the hippocampus, the formation and retention of new memories and the storage and retrieval of old memories are severely impaired (producing anterograde and retrograde amnesia respectively). Such individuals have very short attention spans, are unable to remember items just seen, have graded retrograde amnesia, and have impaired spatial location and navigation ability. In Alzheimer's disease, the hippocampus may be one of the first structures affected, with memory impairments and disorientation the first symptoms appearing. Damage to the hippocampus and the production of these symptoms may result from anoxia, encephalitis, medial temporal lobe epilepsy, alcoholism, and taking certain drugs.

Amygdala

It is interesting to note that the hippocampus receives input from the amygdaloid nuclei and orbitofrontal cortex. These areas play a critical role in the expression of emotions (Sieb, 2013). The amygdala also mediates the strengthening effect that emotion has on episodic memory. If one is aroused or emotional in any way, memory of experiences is greatly increased (Sieb,2013). The amygdala has been implicated in the acquisition and expression of classical (Pavlovian) fear conditioning (a form of conditioning of emotional responses) and LTP appears to be involved (Amunts et al,2005;Blair et al,2001;

Helmuth,2003;Marin,1999;Pare et al,2002;Paton et al,2005; Sapolsky,2003). The amygdala is also involved in appetitive (positive) conditioning (Blair,2008;Paton et al,2005). The amygdala plays a primary role in the formation and storage of memories associated with emotional events and it appears to be the role of the amygdala to regulate memory consolidation in other brain regions (Marin,1999). The amygdala has many connections with the hippocampus (more going to the hippocampus than received from it-Ben Best,The amygdala and the emotions, *Anatomical Basis Of Mind*,Ch.9,see website) and emotions can facilitate the encoding of memories (Gasbarri & Tomaz,2012). Increased amygdala activation immediately after an event increases the strength and retention of memory of that event (Asari et al,2010;Hutcherson et al,2008;Nathan et al,2006;Pare et al,2002). The more emotionally-arousing the event, the greater is the activation of the amygdala (especially the basolateral nuclei) and the greater the strength and retention of the memory of the event. Injections of cortisol and adrenaline and stimulation of the amygdaloid nuclei facilitate memory. Excessive or prolonged stress (with prolonged cortisol release) may hinder memory. Patients with amygdaloid damage are no longer able to better remember emotionally-charged words than non-emotionally-charged words.

Factors Affecting Episodic Memory

A number of factors affect episodic memory. Among these are the effect of spacing rehearsal over an extended period of time, cramming, the Zeigarnik effect (people remember interrupted or uncompleted tasks better than completed ones), use of certain odors, size of the knowledge base (children may be able to remember things better than adults because they have a smaller knowledge base), retroactive interference (learning new information causes one to forget old information), proactive interference (learning one piece of information makes it harder to remember similar new information), emotion (or stimulation of the amygdaloid nuclei), increasing the supply of oxygen to the brain, staying intellectually active, keeping physically active, socializing, reducing stress, getting regular sleep, avoiding depression and emotional instability, and observing good nutrition.

Conclusion

Episodic memory is a four-dimensional record of personal past experiences. This is evident during episodic memory recall. Episodic memory recall entails the retrieval of a particular

four-dimensional organization of conscious experiences: some conscious experiences occur simultaneously, but in different locations; while other conscious experiences occur at the same location, but at different times. Such organization indicates that both space and time must be considered together in the organization of episodic memory recall. Because conscious experiences make up the content of episodic memory recall, episodic memory recall requires consciousness (conscious recollection is required to demonstrate episodic memory), as conscious experiences make up the content of consciousness. It is interesting to note that consciousness at any one time has a similar four-dimensional organization of conscious experiences (some conscious experiences occur simultaneously, but in different locations; while other conscious experiences occur at the same location, but at different times).

Conscious experiences which occur simultaneously, but in different locations in episodic memory recall and consciousness, are reminiscent of space-like spacetime interval separation of events in four-dimensional spacetime, as described by Einstein's special theory of relativity. Similarly, conscious experiences occurring in the same location, but at different times in episodic memory recall and consciousness are reminiscent of time-like spacetime interval separation of events in four-dimensional spacetime, also as described by Einstein's special theory of relativity. Hence the organization and relationships of episodic memory recall and consciousness at any one time may be described utilizing the concept of invariant spacetime intervals as predicted in Einstein's special theory of relativity. This suggests that episodic memory is encoded in four dimensions in order for its recall to have a four-dimensional organization. Hence episodic memory is encoded in four dimensions in the hippocampus via the prefrontal cortex-inferior parietal cortex-inferior temporal cortex-perirhinal cortex-entorhinal cortex-hippocampus pathway. Working memory appears to access the hippocampus via this pathway for the four-dimensional encoding of episodic memory in the hippocampus. Working memory consists of the positive feedback interaction between the prefrontal cortex and inferior parietal cortex. Conscious experiences appear to arise in a nonlinear emergent manner from this positive feedback interaction (working memory). Working memory is the holding in mind of a small number of pieces of information for a short period of time and their manipulation. Positive feedback and nonlinear emergence results in the formation of explicit stable states (conscious experiences). The pieces of information that are maintained in working memory for a short period of time thus appear to be a

number of explicit stable states or conscious experiences. Consciousness, at any one time, and episodic memory recall have the same basic four-dimensional organization of conscious experiences. The organization of both consciousness and episodic memory arises from input from the prefrontal cortex and inferior parietal cortex (from working memory). Hence the four-dimensional organization of consciousness and episodic memory must come from working memory. The information persistence component of sensory memory (such as iconic memory) is the main contributor to working memory. Information persistence is a brief representation of abstract properties of sensory stimuli, such as spatial location, temporal occurrence, and spatiotemporal separation. Information persistence may guide the organization of conscious experiences in working memory via the prefrontal cortex and/or inferior parietal cortex. Sensory memory, working memory, short term memory, and long term memory operate together in the development of episodic memory. The encoding and retention of episodic memory involves the establishment of LTP in place cell assemblies of the hippocampus by working memory. This encoding and retention of episodic memory involves STDP and other mechanisms of homeostatic intrinsic plasticity working together to mould, stabilize, and optimize neural connections. Working memory accesses the hippocampus via the prefrontal cortex-inferior parietal cortex-inferior temporal cortex-perirhinal cortex-entorhinal cortex perforant path to encode an allocentric four-dimensional viewpoint dependent representation in the CA3 region of the hippocampus. Grid cells, head direction cells, and boundary cells of the entorhinal cortex are responsible for the encoding of this representation in four dimensions in place cell assemblies of the CA3 region of the hippocampus. This encoding is a static four-dimensional neural (cognitive) map of the environment. The CA3 region then sets up an allocentric viewpoint independent representation in place cell assemblies of region CA1 of the hippocampus. This is a representation of the dynamic relationships arising from CA3. The representations in CA3 and CA1 in sync make up the complete episodic memory and must be reactivated in sync for episodic memory recall, imagination, and future ideations.

Consciousness and episodic memory are linked by working memory. They are both organized by working memory. Episodic memory is associated with consciousness via working memory. Consciousness and episodic memory recall are frames of reference (observational perspectives). Hence they both have a subjective or perspective-like aspect. Their four-dimensional organization gives them a "picture" or "image-like" quality. The

simultaneous production of conscious experiences at different locations in consciousness and episodic memory recall provides a four-dimensional awareness of our surroundings and of our self in relation to those surroundings. The production of conscious experiences at the same location, but at different times in consciousness and episodic memory recall, provides us with a four-dimensional awareness of dynamic changes in our surroundings and of cause and effect relationships occurring in those surroundings and of our self and those surroundings. Syncing of these two types of awareness in four-dimensions enable the more effective production of appropriate voluntary (adaptive or goal-directed) actions. Because of four-dimensional episodic memory, we can more effectively look toward the future or use our imagination. This greatly improves our success and survival in our complex societies. These processes would be much less effective if they were not four-dimensional.

The utilization of relativistic principles in human consciousness and memory offer a different avenue of support for the validity of Einstein's theories of relativity. This suggests that our brain may create and remember its own four-dimensional reality.

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