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OSCILLATORY HERITAGE OF THE GRASTYÁN SCHOOL

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Two major structural designs characterize the cerebral cortex: the scalable, modular neocortex and the single-module hippocampus. Functions attributed to the hippocampal formation have varied over the past several decades and include episodic memory in human lesion studies, spatial mapping in single unit recordings and voluntary exploration of the environment in field recording studies in animals. I suggest that the common thread across these parallel developments is that each captures the essence of episodic coding: items are organized in spatio-temporal context. I suggest that theta oscillations, studied extensively in the Grastyán school in Pécs, is the key temporal metric. Ordered sequences of items are encoded by the strict temporal relations of hippocampal cell assemblies nesting within cycles of theta oscillation. Such a temporal compression mechanism brings neuronal assemblies together in the time window of synaptic plasticity and allows the linking of first order (neighbor) and higher order relations. Seven to nine interleaving assemblies, representing overlapping past, present and future items, can be combined into an episode in a single theta cycle. During recall, the entire hippocampal connection matrix can be searched in the time period of the theta cycle (120–140 msec). I suggest that the hippocampus is an efficient search engine for the reconstruction of complex episodes from fragmentary information.

Keywords: memory, cell assemblies, random graph, autoassociator, unit activity, Pécs, Hungarian, hippocampus, brain oscillations, voluntary

What Makes Us Individuals?

When it comes to the complex organization of the brain, we tend to think of the large cerebral cortex. Its structure and the functions its anatomical organization supports are tuned mainly to detect orderly, species- and individual-invariant relationships in our environment. The perceptions of natural scenes, speech and music, body image as well as our occasional illusions can be attributed largely to the unique organization of the isocortex. Brains with these features only would be useful as long as they are embedded in an unchanging environment. However, we

live in an ever-changing world and numerous events, relevant to our survival and happiness, occur independent of us in an idiosynchratic manner. Detecting and storing all random events and relations around us are virtually impossible by any imaginable hardware. Furthermore, perception and storage of all that junk does not have any personal significance, anyway. Except the ones that do. Our names, birthdates of loved ones, and other important family events are our unique experiences, which do not simply unfold by some external rules. Such arbitrary associations must be first internalized in our brain for later retrieval to assist in future evaluations and decision-making. Forming and storing of individual experiences create a knowledge base, a unique brain-based context that modifies the way the neocortex processes future sensory experiences and contingencies. The accumulation of past experiences, collectively called memory, is responsible for creating individual identity. The emergence of individuality and personal identity are therefore strongly linked to mechanisms that enable the animal to recollect the past and modify its future behavior on the basis of these recollections. There is nothing in the physical world that would tell us whether a face is pleasant or repellent to us. The same face may be judged as beautiful or ugly on the basis of cumulative past experiences of the different observers (Buzsáki, 2004).

What are these experiences and where are they stored? Experiences stored in the brain are usually divided into two major categories: implicit and explicit. An engineer would call them automatic and supervised. For a psychologist, the term explicit or "declarative" means that such experiences have "conscious" recollections and can be declared verbally. They include life-time episodes unique to an individual, such as our first date, or the births of our children, or learning arbitrary facts related to the world we live in, such as the distinction between the brain structures neocortex and hippocampus. These latter factual or semantic memories lack a unique personal link. In contrast to these consciously experienced memories, the implicit experience of learning how to walk comfortably in high heel shoes or habituation to the annoying sound of the traffic when living next to the highway does not require that we are aware of the process (Squire, 1992).

Forming and storing arbitrary associations requires a suitable structure with a large number of connections randomly organized. The six-layer neocortex with its regular modular architectonics and mostly local wiring is far from ideal for such a task. A large part of the modularly organized neocortex is tuned to extract statistical regularities of the world conveyed by our sensors. But there is another piece of cortex, the "other cortex," or, in our Hellenistic scientific jargon, the allocortex below and medial to the neocortical mantle. As I will argue, the hippocampus contains a large arbitrary synaptic "space," which is ideally built for the construction of episodes and temporal sequences from arbitrary relations.

Hypothesized Functions of the Hippocampal System

Starting with the famous patient H. M. with bilateral surgical removal of the hippocampus, a consensus emerged among human psychologists that the hippocampus and associated structures are responsible for declarative (episodic and semantic) memories (Scoville and Milner et al., 1957). However, the mechanism of encoding and retrieving information has remained a major challenge for future work.

A major hurdle has to do with the definition. Episodic memory is claimed to be uniquely human, which endows the individual with the capacity to reference personal experiences in the context of both time and space (Tulving, 1987). It is these life-long experiences, representing unique events through space-time that give rise to the feeling of the self and are the source of individuality. Singular episodes can reemerge through the process of free recall. With such definition, how are we expected to work out physiological mechanisms of declarative memories in animals simpler than humans? Not surprisingly, hippocampal research on animals gave rise to different perspectives. Among these, the discovery of "place cells" provided the most important insights into hippocampal function (O'Keefe and Nadel, 1978). Place cells explicitly characterize positions in the environment, independent of animal's location. These landmark-controlled place-signaling neurons are used by the brain to create navigational maps, a Cartesian space, of the environment. Allocentric, map-based navigation is essentially a geometric triangulation process, which depends primarily on the perceptual (input) properties of the brain, a method that does not require motor output or a temporal context. Although the original formulation of the cognitive map theory implied that addition of a temporal component to the basic spatial map in the human provides the basis for an episodic memory system, the relationship between the essentially egocentric episodic memory and allocentric landmark navigation has remained a controversial issue. What is the source of the temporal component that can serve such an important role? A third line of investigation may provide a clue here. The most prominent electrical pattern of the hippocampus is the rhythmic theta oscillation at 6–9 Hz (cf. Buzsáki, 2002), which may provide the necessary timing.

Perhaps reformulating the definition of episodic memory might be instructive here. In its simplest possible formulation, episodic memory can be simply defined as: *What* happened *where* and *when*? From this perspective, the different lines of thoughts regarding the mechanisms of the hippocampus can be tied together, with the place cell and theta oscillations providing the spatio-temporal context, a critical aspect of episodes. Storing large number of arbitrary events requires special structure, for which the random wiring of the hippocampus is most suitable. Be-

low we attempt to put these ingredients together. Because the ground work for this venture began in Hungary, a short digression for exploring the seeds of the ideas is justified.

The Hippocampal Theta Link to Pécs: Grastyán's School of Neurophysiology

My connection with brain rhythms began with attending a physiology lecture by Endre Grastyán in the beautiful small town, of Pécs on the sunny slopes of the Mecsek mountains in Hungary. University of Pécs, or Universitas Quinque Ecclesiensis, as it was called when it was founded in 1367, has produced a remarkable set of neuroscientists, including János Szentágothai, a world-class neuroanatomist, Béla Flerkó and Béla Halász, pioneers of neuroendocrinology and Ferenc Gallyas, the creator of the widely used silver impregnation methods for neuronal labeling.

Like many of us at a young age, Grastyán could not quite make up his mind in his twenties about his future. Finding nothing too interesting or challenging initially, he decided to train for the protestant priesthood and to get some orientation in philosophy. But his mind, filled with too much curiosity, prevented him from becoming a preacher. He ended up in medical school during those stormy years around World War II and became the assistant of Professor Kálmán Lissák. This was a good start. Lissák, a student of Otto Loewi in Graz, Austria, was a legendary surgeon-physiologist. I vividly remember one of his lectures, operating on a dog in front of a class of two hundred students, talking to us constantly about the various neuronal regulating mechanism of blood circulation while effortlessly preparing all the nerves, cannulating veins and arteries and hooking up the instrumentation. At some later point in my early career, Lissák came into my physiology *practicum* and saved me from a complete humiliation from my students. I was trying to demonstrate the classic experiment of Loewi, the first proof that a chemical is released at the synapse. This most beautiful experiment requires two frog hearts. The demonstration, if done well, is simple, elegant and convincing. In the original experiment, Loewi placed the hearts into salt water and separated them by a membrane. He found that stimulation of the vagus nerve that innervates the heart slowed the rate of the stimulated heart but had no effect on the unstimulated one. After removal of the membrane, however, stimulation caused both hearts to slow down. His interpretation of these data was that nerve stimulation caused the release of a substance from the nerve endings, which he called "Vagusstoff", i. e., "stuff from the vagus." This chemical then acted on both hearts. Loewi described his observations in a short paper of only four pages in 1921, which laid down the chemical theory of synaptic transmission. For this breakthrough he was awarded

the Nobel Prize in physiology and medicine in 1936. His student Kálmán Lissák, in his best days, had the reputation of being able to perform Otto Loewi's experiments even blindfolded. He was a tall, attention-demanding handsome man with white hair, who wore a bow-tie even in the worst days of the Bolshevik drama. Visiting my seminar that day, he promptly recognized my troubles. Without saying a word, he took two new frogs, prepared the hearts and nerves in no time, placed them in front of me and left the room. With two great preparations in my hand, the demonstration worked well. My embarrassment notwithstanding, I proudly explained to the students how the chemical acetylcholine, released by the stimulated nerves, was responsible for the visible slowing of heartbeats. After the *practicum,* I prepared 6 heart pairs, and the last three worked just like the ones I got from Professor Lissák. From then on, Loewi's experiment on neurotransmitter release became one of my favorite demonstrations.

Although Endre Grastyán was perhaps the closest friend of Lissák, the two men were as different as they could be. Apart from the surgery demonstrations, Lissák's lectures were scarcely attended. In contrast, Grastyán was a performing artist, his lectures were carefully composed and choreographed. The lecture room was always packed and even students from the neighboring Law School came to listen to his mesmerizing lectures. He generated so much enthusiasm that we students became convinced that the issues he discussed every time were the most important ones in the universe. I often thought that Grastyán could have been a novelist, a story-teller, an artist, and a musician, all in one person. There lay in him, beneath the surface of science, a lost Atlantis of philosophy, fine arts, musical talent and a unique human interaction that one thinks co-existed only in the long-extinct great men of the Renaissance era. On that particular lecture in April, 1970 he talked about the role of control, a topic that changed my life for good. My high-school plan to become an electric engineer had been vetoed by my parents, who offered me the choice between Medical School and Law School. While my friends were having fun at the School of Engineering in Budapest, learning exciting stories about radio transmission and electronic oscillators, I spent most of my time studying the unending details of bones and ligaments. But in that spring time lecture, Grastyán was talking about some truly intriguing questions. His key idea was that control in living systems begins with the output. The first simple biological systems did not have any inputs; they did not need them. Generating a motor output was sufficient when food was abundant in the sea environment. Rhythmic contraction of muscles guaranteed that some nutrients were obtained. Sensation of direction and distance developed only after the invention of movement across space. There is no need to perceive anything unless one can act upon the perceived input, Grastyán argued. He provided numerous and vivid examples of how sensation and perception are always subordinated to motor organization. The whole complicated brain web serves to supervise the output, which in his thinking in-

cluded skeletal movement, autonomic responses, motivation, emotion and even thought. There is no use to hear without the ability to orient to the source. What is the point of the great smell of food if we cannot eat it? The idea of output control of sensation is a profound thought even today. Back then, when Pavlovian sensory-sensory association was the dominant ideology in the East and stimulus-decision-response paradigm dominated Western thinking, Grastyán's teachings were unusual, to say the least. After his lecture I rushed home to read the relevant chapters in our official textbook only to realize that there was not a single word there about what I heard that morning. Or in any other books, as I learned after feverishly searching for sources and references in the university library. Nevertheless, beginning with Grastyán's lecture on the emotional organization in the brain, my life in medical school assumed a new meaning. I applied to become his apprentice and spent most of my student life in his lab. Training in Grastyán's laboratory meant mostly to be part of fascinating lunch discussions that often went on for several hours, where topics ranged randomly from homeostatic regulations of the brain to Johan Huizinga's "Homo Ludens". It was during these lunch lessons where I first learned about the hippocampal "theta" rhythm, the oscillation that became my obsession ever since. Before discussing the critical role of theta rhythm in providing a temporal context for episodic memories, we should overview the structural requirements of an effective coding-decoding device.

A Large Random Graph for Storing Episodes

The hippocampus is a one-layer cortex, a sort of a large appendage to the neocortex. Its main input and outputs are the same: the neocortex, which communicates with the hippocampus via the entorhinal cortex. Unlike the modular neocortex, it is a single giant cortical column. The major entry point to the hippocampus is the granule cells of the dentate gyrus. The axon terminals of granule cells excite about half of the hippocampal pyramidal cells, which are clustered together in the CA3 region (Acsády et al., 1998). In turn, the CA3 neurons send their main collaterals to the CA1 pyramidal cells. These connecting axons are known as Schaffer collaterals, named after the Hungarian anatomist-neurologist Károly Schaffer, who discovered them. The remaining collaterals, form the largest recurrent collateral system in the brain, return the excitatory information to partner CA3 neurons. Due to this large recurrent and feed-forward system, 90% of all intrahippocampal synaptic contacts are formed by the CA3 neurons. The hippocampal information returns to the entorhinal-neocortex origin by the projecting axons of the CA3 pyramidal cells. This neocortex-hippocampus-neocortex loop is an epitome of the multiple, parallel organization of the cerebrum. Traffic in this excitatory system is under the strict control of a rich family of inhibitory neurons

(Freund and Buzsáki, 1996; Sik et al., 1994). This integration of information in the short and long loops depends on the available time windows. Such diverging and converging reverberating circuits can serve various functions, including error correction, pattern completion, amplification and temporary storage. This is what the hippocampus is about. Permanent memories are then laid down in the neocortex, due mostly to the sleep-related activity patterns of the hippocampus (Buzsáki, 1989).

To illustrate the physiological operations of the hippocampus, let us assume that the neocortex is a library and we have to search for a book in it. An ideal library not only contains most books ever written but it also allows speedy access to any volume accurately. Unfortunately, there is no ideal library, man-made or biological. The more books that are accumulated in the library the higher the overlap among authors' names, titles and content. Searching for an item in such a colossal library can become a nightmare. Finding Imre Madách's *Tragedy of Man* is straightforward because of the unique key words one can supply. But try to find the book that you remember is about honesty, courage, and involves a team of young boys fighting a "West Side Story" kind of turf battle over a derelict Budapest building site and about honor. The main character dies for his idols and team because he acquires pneumonia after spying on the enemy team by hiding in the cold lake of a public garden. Even the best man-made search engine, the internet may fail in the search. After typing in multiple combinations of numerous key words about the story, the search engine Google may give you a million choices. However, if you ask your educated librarian, chances are that he or she can tell you right away that the book you are desperately looking for is "The Pál Street Boys" by Ferenc Molnár, who was perhaps the greatest playwright to come out of Hungary. The reason for such a huge difference in search efficiency is that your librarian has a hippocampus, whereas Google does not. Thanks to the hippocampus, humans are very efficient in storing and remembering episodes. We can search the huge space of the hippocampal index and construct a full story from fragments in a matter of a few theta oscillatory cycles.

How big is the available abstract space in the hippocampus and how is it organized? Together with Peter Somogyi, from Oxford University we set out to study this important question by labeling single neurons in the intact rat brain and reconstructing the entirety of their axon collaterals and synaptic contacts in three-dimensional space. The 200,000 CA3 pyramidal neurons in each hemisphere of the rat brain posses a total of 40 kilometers axon collaterals and an estimated 5 to 10 billion synaptic contacts in each hemisphere (*Fig. 1;* Li et al., 1994). Unlike the mostly locally organized neocortical neurons, the distribution of the contacts in the recursive and feed-forward projections in the hippocampus is reminiscent of a random graph. The concept of random graph implies that one can walk from any neuron to any other neuron along the calculated shortest possible synaptic path,

Figure 1. Hippocampus: a randomly organized synaptic space. Shown is the axonal arbor of a single CA3 pyramidal cell. Cell body is indicated by the asterisk. A, anterior; P, posterior direction. Note extensive, non-local distribution of the axon collateral. An average CA3 neuron has about 300 mm of axon collaterals, which establish 30–60,000 synapses with other CA3 and CA1 neurons. Such strongly connected graph is an ideal autoassociator

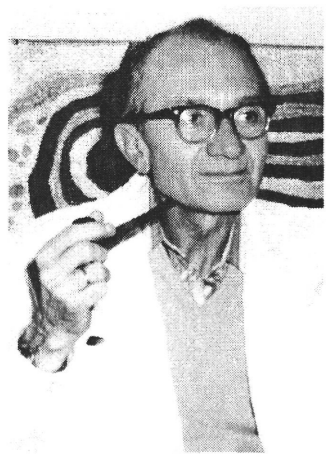
much as one can walk in an unobstructed field from any place to any other place (Erdős and Rényi, 1959; Barabási, 2002). Construction of a full random graph from 200,000 CA3 pyramidal cells would require only 15 to 20 divergent connections from each cell. This small figure is in stark contrast to the 10,000 to 20,000 of synapses an average CA3 pyramidal cell establishes with its peers. The large divergence implies that the number of possible routes between any randomly chosen start and goal cells is a truly galactic figure. Nevertheless, no matter how impressive this figure is, we do not get far with such reasoning alone. This is because synapses between pyramidal cells are weak and the discharge of a single starter cell will not be able to fire any of its target peers. Only discharging neurons can be used for encoding and retrieving of memories. Without speculating further we can register that the CA3 autoassociator is a strongly connected, directed and weighted graph. This arrangement simplifies how activity can spread in the recursive network. Instead of spreading excitation in any direction randomly, the trajectory of activity is strictly determined by the synaptic weights so when activity arrives at a bifurcation choice, it will progress along the path with the stronger synapses. Importantly, the synaptic weights are set by experience during the learning of episodes. As discussed above, a library to be useful should contain not only all the books we will ever need but also an efficient search mechanism that allows the retrieval of books in a short time. This is where temporal packaging of

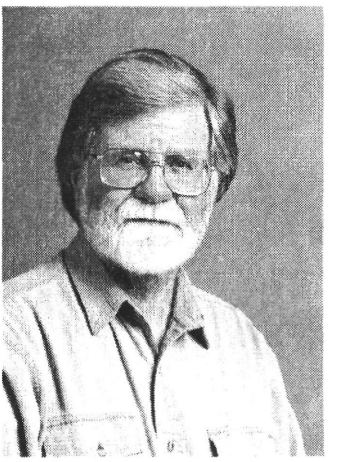
information becomes critical. I speculate that the packaging mechanism is hippocampal theta oscillations.

The Short Story of Theta Oscillations

The story of theta oscillations is an edifying chapter in the history of behavioral-cognitive neuroscience. The controversy regarding the exact behavioral correlate(s) of theta oscillation has raged for decades, generating numerous published experiments and occasional strong feelings among the contestants. Virtually every conceivable overt and covert behavior has been associated with hippocampal theta activity, as summarized in *Figure 2*. The first experiments in behavior of animals were carried out by Grastyán et al. (1959). According to Grastyán's pioneering work in the cat, theta reflected an "orienting reflex, searching for stimuli with significance to the subject". Although this relationship has been challenged many times, it has remained one of the dominant views about the function of theta. Many other concepts can be placed under the same general rubric of "input processing". In contrast, a number of hypotheses argued in favor of the "output" or motor control role of hippocampal theta. The most influential of these hypotheses has been the "voluntary movement" hypothesis of Vanderwolf (1969). Cornelius (Case) Vanderwolf, my postdoctoral adviser, suggested that theta occurs only during intentional or voluntary movement, as opposed to immobility and "involuntary", i.e., stereotypic activity. Despite seven decades of hard work on rabbits, rats, mice, gerbils, guinea pigs, sheep, cats, dogs, old world monkeys, chimpanzees and humans by outstanding colleagues, to date, there is no widely agreed term that would unequivocally describe behavioral correlate(s) of this prominent brain rhythm. By exclusion, the only firm message that can be safely concluded from this brief summary is that in an immobile animal no theta is present, provided that no changes occur in the environment, and the animal is not "thinking".

Why is it so difficult to agree on the behavioral correlates of such simple mechanisms as a brain oscillation? Processing environmental inputs requires "attention", and so does intentional movement. With the introduction of the term "voluntary", theta oscillation research unintentionally entered the territory of "intentionality," a label that refers to the "substance" of all subjective mental activity (Dennett, 1987). Thus, an inescapable deduction from the behavior-brain correlation approach is that the "will" plays a critical role in theta generation. An alternative, and perhaps more sober, conclusion is that our behavioral-cognitive terms are simply working hypothetical constructs that do not necessarily correspond to any given brain mechanism. Although the true goal of neuroscience research is to reveal how the brain generates behavior and how particular mechanisms, such as





Movement
Running
REM sleep
Whisking
Muscle activity
Instrumental response
Operant learning
Sniffing
Whisking
Memory
Response inhibition
Response persistence
Approach
Avoidance
Conditioning
Gape response
Voluntary movement
Learning
Extinction
Orienting
Temperature change
Autonomic-somatic
Olfaction
Reversal learning
Motivation
Information processing
Decision making
Visual search
Neurosis
Arousal
Orienting
Attention
Volition
Comparator
Arousal Arousal Mismatch
Frustration
Anxiety
Aggression
Holography
Cholinergic response
Sexual behavior
Memory
Response persistence
Habituation
Conditioning
Avoidance
Sensorimotor
Defense
Bar pressing
Activation
Readiness
Swimming
Play
Hypnosis
Working memory
Plasticity
Encoding
Retrieval
Mapping
Navigation

1930 40 50 60 70 80 90 2000

Figure 2. Hypothesized functions of hippocampal theta oscillations during the past several decades. Most correlates can be lumped as "sensory-attention" (input function) or motor output function. Endre Grastyán's (left) 'orienting response' hypothesis was the first, which was derived from observations in behaving animals (cat). The most influential hypothesis in the rat has remained the 'voluntary movement' correlate by Cornelius (Case) H. Vanderwolf (right). Note the large variety of the hypotheses and their culmination in the 1970s. The behavior (independent variable) - brain mechanism (dependent correlate) approach failed to produce a consensus on the behavioral significance of theta oscillations

theta, can categorize and define behaviors, most behavioral-cognitive research, to date, seems to work the other way around. We take a man-created word or phrase, such as one of those in the above list, and search for brain mechanisms that may be responsible for the generation of the conceived behavior. In my humble opinion,

such approach has limitations, despite the best intentions. For example, Vanderwolf used sophisticated "ethological", fine-grain analysis of behavior. Ironically, it is through his work that theta became linked with free will. Grastyán objected passionately against the term "voluntary", yet he could not avoid its connotations. We never uttered Vanderwolf's name in Grastyán's lab without adding a curse, an "innocent" Hungarian custom. Grastyán dedicated the last decade of his life to the understanding of the neurophysiological substrates of play behavior and concluded that theta is an invariant correlate of play in kittens and cats. Paradoxically, according to his favorite philosopher, Huizinga (1955), play is "a voluntary activity or occupation executed within certain limits of time and place".

An alternative strategy to understand the role of theta oscillations in behavioral organization is to reveal its content. By content I mean the synaptic and cellular mechanisms that give rise to a population 'order parameter' measured by the mean field of theta waves. Through this process we can gain insight into the temporal organization of population activity of single neurons (Buzsáki and Draguhn, 2004). It is the time metric of hippocampal rhythms that determines the synaptic interactions within and among cell assemblies (cf. Buzsáki 2002). If the population activity of the hippocampus provides a timing mechanism and single hippocampal neurons are active depending on the spatial position of the animal, how do we exploit these mechanisms in the service of episodic memory?

Encoding of Episodes by Theta Oscillation-embedded Packages of Neuronal Assemblies

My suggested solution to the above dilemma is the following. If episodic memory in humans provides some internal rules of its organization, we should be looking for such rules in the physiological patterns of neurons in animals. Beginning with the seminal work of Pál Ranschburg from Pázmány (now Eötvös) University in Budapest before World War II, it has been clarified that episodes are not simple linear chains of events, such as A is followed by B, B is followed by C, etc. If it were the case, episodic memories would be extremely vulnerable and losing one item would terminate the episode. Instead, we know from experience that the essence of episode telling is that the story can evolve in multiple directions. This is possible because in addition to the first order (immediate neighbor) relations, higher order connections are also coded (Kahana, 1996). In episodic learning, stronger associations are formed between stimuli that occur near each other in time compared to those that are separated by a greater interval. Furthermore, forward serial associations are stronger than backward associations, meaning that once an item from a studied list is retrieved, the likelihood of retrieving the next item is twice as probable as retrieving the preceding item. Encoding is better for-

ward in time. Looking ahead of the model, we hypothesize that neuronal mechanism of episodic encoding is the tightly correlated timing of neuronal firing. This timing mechanism and the large arbitrary connection matrix of the hippocampus can insure that not only immediate neighbors but items with larger distances can also be connected. What we need for testing this hypothesis is to investigate the neuronal mechanisms in behaving animals in situations analogous to the learning of episodes in humans. Without attempting to prove each step of the logic with complicated experiments, here is a short synopsis of the events that might be occurring in our hippocampus during the formation of episodic memories. (For a more detailed treatment of the topic, see Buzsaki, 2005; 2006.)

Episodic learning of serially presented items, such a list of words, or in real life situation a story, is analogous to a rat's behavior running on a linear track for water or food reward and encoding the sequentially observed places. Place encoding requires sequential activation of hippocampal place-encoding cells in a temporal context *(Fig. 3)*. Sequential segments of the track are represented by unique sets of hippocampal place-coding cell assemblies (O'Keefe and Nadel, 1978), which are bound together by synaptic interactions into an episode. The metric distances between adjacent place representations of two place-coding assemblies are reflected by the strength of their synaptic connections and can be studied experimentally by measuring the time differences between the assemblies within the theta cycle. The way this coding occurs is a fascinating but complex process.

Each assembly is active maximally only once on the track, signifying a given position. However, instead of coding each spot in a narrow time window only once, place representations of neurons have long "tails", reflected by the elongated size of the place field, an average of 30–40 cm. As the rat enters the field, the firing rate of the neuron begins to increase, reaches a maximum in the middle of the field and then it decreases gradually as the rat leaves the place field of the neuron. The firing rate of the neuron is controlled by two parameters: the distance from the place field center at a longer scale and periodically by the phase of the theta cycle (O'Keefe and Recce, 1993; Harris et al., 2002). Because each consecutive part of the track is represented by an assembly of neurons, this results an interesting scenario. First, each cell assembly represents one spot best but has some progressively weakening say in the representation of the previous and future places as well. At each theta cycle, the rat moves about 5 cm, so that each place field is re-represented 6 to 9 times. Second, although each spot is represented best by one cell assembly, another 5 to 8 assemblies also contribute. The result is that in each theta cycle 6 to 9 assemblies are packaged, representing the past and future positions on the track in a time-compressed manner (*Fig. 4;* Skaggs et al., 1996). This temporal compression is the most critical aspect of the coding mechanism because it brings neurons representing distant places into the time-frame where synaptic plasticity operates. Single neurons or pairs of neurons cannot represent

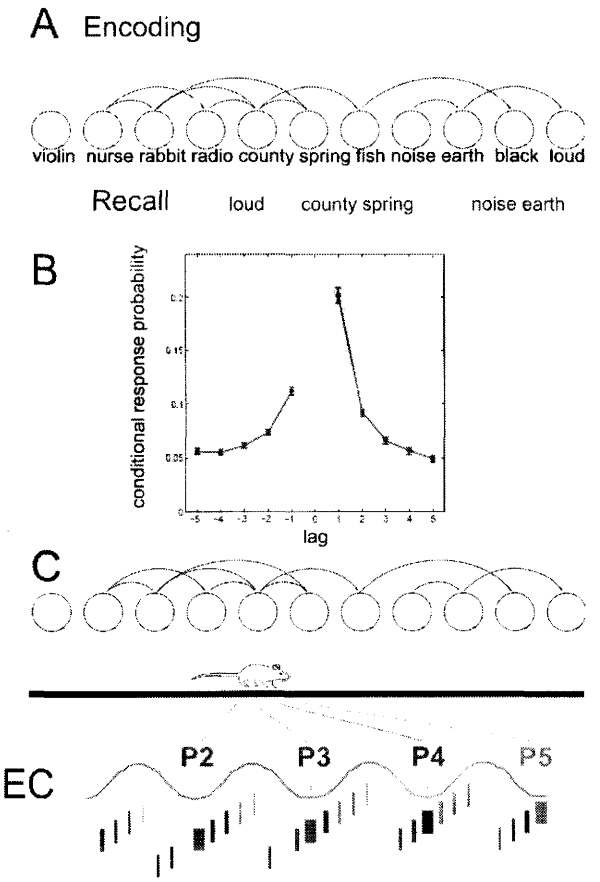


Figure 3. Analogy between episodic learning and 1-dimensional navigation. (A) Learning and free recall of an episode. Arrows, higher order relationships, which facilitate recall of items with nearby positions (e. g., county spring, noise earth). (B) Conditional response probability of recall as a function of positional lag. Note advantage for recalls to nearby serial positions and an asymmetry favoring forward recall. (C) Model of episodic encoding in the hippocampus. The width of the bars indicates firing rates of the assemblies and the temporal differences between assemblies reflect distances of their spatial representations. EC, input from the entorhinal cortex (arrowheads) provides updated information about the external environment (places, P1 to P5). In each theta cycle, 6 to 9 cell assemblies are compressed in the order which the rat explores the subsequent places of those assembly representations. In each cycle the most active assembly is associated with the through of the theta oscillation. The compression mechanism provides a context for the strongest assembly and its represented item. Each assembly is re-represented in 6 to 9 subsequent theta cycles, corresponding to approximately 1 sec of activity and 30–40 cm travel distance. The temporal distances within the theta cycle determine the synaptic strengths between the assemblies. By this mechanism both first order (neighborhood) and higher order distances can be connected, which allow episodes to evolve in multiple directions. In the absence of environmental or body cues (i. e., free recall), assemblies are advance by the previous cycles (e. g., P1 recalls P2)

times longer than a few hundred milliseconds, and synaptic plasticity works at the tens of milliseconds scale. The compression mechanism makes it possible that the representations of items can be translated into synaptic strengths among neurons and assemblies.

In related research we have established that the life-time of each hippocampal assembly is about 10–20 msec (Harris et al., 2004). Neuronal coalitions are formed preferentially at this temporal scale because this time window is the most efficient to affect target assemblies. This time constraint allows only 6 to 9 cells assemblies to be nested in the time period of the theta oscillation (120–140 msec), that is we arrive at the same numbers of assemblies as we did with our behavioral estimation. Physiologically speaking, the theta oscillation corresponds to the build up of excitation in the hippocampal space, while all neurons can be visited and terminated by the recruited inhibition. In other words theta periods are temporal windows of opportunities to search the entire hippocampal space. Assemblies are reflected by their time differences within the theta cycle.

The sequences are stored in the autoassociative CA3 recurrent and CA3-CA1 collateral systems and can be updated by entorhinal cortex-mediated environmental signals. During memory retrieval, the CA3 autoassociator is searched in each theta cycle, recalling 6 to 9 temporally linked cell assemblies each representing a spatial field that the rat would traverse during the next second or so. The predicted and perceived locations are replayed in tandem by the CA3 and CA1 assemblies. Prediction of future locations is possible because distances are encoded in the synaptic strengths between assemblies (Muller et al., 1996) and reflected by their theta time temporal sequences. In short, I suggest that the overlapping past, present and future locations are combined into a single episode by the self-organized CA3 and CA1 assemblies in successive theta cycles. The theta-cycle compression brings not only neighboring but several assemblies together in a time frame that allows the strengthening of their connections simply by their temporal differences. Thus, the physical distances represented by the cell assemblies in the real world are translated to time and phase within the theta cycle and eventually synaptic connectivity. This simple mechanism can account for the first- and higher order linking of items into the same temporal context, represented by a theta cycle.

Of course, all experiments described were carried out in animals, which precluded direct testing of the main hypothesis by free recall. Nevertheless, the model outlined above can account for temporal contiguity and the asymmetric nature of recall in episodic memory at the neuronal level. Even though we studied animals, the spatial behavior and inferences we can make from these observations should apply to episodic learning in humans as well.

The observation of nested cell assemblies in hippocampal theta oscillations deserves a little digression. Our previous work demonstrated that 6 to 9 faster cycles, called gamma oscillations, are nested within the theta waves (Bragin et al., 1995).

The faster gamma cycles therefore can be conceived as the macroscopic reflection of cell assemblies. The theta period would define the span of memory with 7 to 9 items multiplexed on the successive gamma cycles (Lisman and Idiart, 1985). Importantly, in human subjects, the time of short-term memory scanning increases with the set size, corresponding to approximately 25 milliseconds per "to-be-remembered" item. Thus, the number of items that can be stored by the multiplexed gamma-theta model is identical with the "magical number 7 (±2)," the psychophysically measured limit of working memory (Miller, 1956). Therefore, the multiplexing mechanism described above may be responsible for providing a buffer for short-term memories, a process attributed to the operations of neuronal circuits in the prefrontal cortex. Because we also found that the magnitude of gamma oscillations in the prefrontal cortex are modulated by the phase of hippocampal theta oscillations, the common multiplexing mechanism would provide a physiological link between working memory and episodic memory.

What Did We Learn?

Now we are in a position to define theta oscillations from the brain's point of view. Experiments with single cells and cell assemblies we briefly discussed show that the quantal theta periods are necessary for chunking events and places together in time so that the participating neuronal assemblies can be tied together. The temporal compression of cell assemblies in combination with the rules of synaptic plasticity allows for activity to jump from one assembly sequence to the next. Thus, from the perspective of the brain, Grastyán's theta oscillation is an essential temporal organizer, a metric that relates synaptic strengths to the changes in the outside world. Theta is the temporal means of navigation in both neuronal space during episodic memory and real space during self-motion.

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