CONSCIOUS EXPERIENCE, THE NEURAL MECHANISM

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Abstract: The physical basis of conscious experience is revealed by direct observation and analysis of any conscious experience. Human conscious experience has an invariant structural mode of organization based on the three types of space-time intervals (light-like, time-like, space-like). Sensory input activates the autonomic nervous system, endocrine system, and ascending reticular activating system to produce the awake conscious state. The dorsal and ventral frontoparietal attention networks are activated. Dorsal and ventral cortical functional streams carry "what", "where", and "when" information to the medial temporal lobe for the encoding, storage, and recall of conscious experience (episodic memory). Hippocampal place cells and time cells encode events in space and time within spatiotemporal contexts conveyed by entorhinal cortex grid cells and ramping cells. Theta phase precession unifies the encoding of space and time and theta travelling waves ensure that the instantaneous output of the hippocampus consists of topographically-organized segments of space and time, space-time intervals. By parsing spatiotemporal contexts into quantal units of where and when events occur, hippocampal neurons bridge, and thereby organize events, in a conceptual organization of events (conscious experience). Space-time intervals are extracted from the hippocampus by the prefrontal cortex for the cognitive, affective, and motivational aspects of conscious experience.

Key Words: space-time intervals, light-like, time-like, space-like, hippocampus, space, time, place cells, time cells, entorhinal cortex, grid cells, ramping cells, theta phase precession, gamma oscillations, episodic memory, emotion, attention, consciousness, dorsal stream, ventral stream, travelling waves, medial temporal lobe, prefrontal, parietal

INTRODUCTION

Consciousness is the awake state. It arises when sensory input activates the autonomic nervous system, endocrine system, and ascending reticular activating system (arousal). Conscious experience makes up the content of consciousness, i.e., what is in consciousness. Human conscious experience has a basic structural mode of organization that is common to all conscious experiences and to all human beings. This is revealed by direct observation and analysis of any conscious experience. One can readily observe that many events in the conscious experience of a room occur at the same time (simultaneously), but in different spatial locations (desk, chair, computer, monitor, printer, keyboard, windows, door, lights, walls, floor, ceiling, etc.). Outside, many events in that conscious experience also occur simultaneously, but in different spatial locations (trees, parked cars, buildings, road, sidewalks, playground equipment, lawns, etc.). In physics, this type of separation of events is known as space-like space-time interval separation; events are separated by space, but not time. Space-like separation is a basic part of the structural organization of all human conscious experiences. One can also observe in conscious experiences that some events are experienced at the same spatial locations, but at different times (people replacing other people in seats or as speakers, replacing a glass with a

cup, any moving object, one conscious experience replacing another, etc.). In physics, this type of separation of events is known as time-like space-time interval separation; events are separated by time, but not space. Time-like separation is also a basic part of the structural organization of human conscious experiences. Events are identified via transmission of light to the eyes. This is called light-like space-time interval separation; events are separated by the distance light travels. Light-like space-time intervals are a basic component of human conscious experiences. Three types of space-time intervals (space-like, time-like, light-like) completely account for the organizational structure (appearance) of human conscious experience.

Three core sources of information (what, where, when) underlie the encoding, storage, and recall of conscious experience (episodic memory). The dorsal and ventral frontoparietal attention networks are activated voluntarily or by sensory salience. Where, what, and when information is conveyed by the dorsal and ventral cortical functional streams to the medial temporal lobe where events are encoded in space and time by hippocampal place cells and time cells within spatiotemporal contexts conveyed by entorhinal cortex grid cells and ramping cells. Place cell and time cell theta phase precession unifies the encoding of space and time in the hippocampus. Place cells and time cells reflect fundamental mechanisms by which hippocampal neural networks parse any spatiotemporal context into quantal units of where and when events occur, bridging, and thereby organizing the events, in a conceptual organization of events (conscious experience). Theta travelling waves ensure that the instantaneous output of the hippocampus consists of topographically-organized segments of space and time (space-time intervals). These are extracted from the hippocampus by the prefrontal cortex for the cognitive, affective, and motivational aspects of conscious experience.

CONSCIOUSNESS

Arousal

Arousal is the physiological and psychological state of being awoken. The reticular formation (RF), especially those neurons of the ascending reticular activating system (ARAS), plays a crucial role in behavioral arousal and consciousness (Saladin, 2018). Arousal occurs through sensory activation of ARAS, the autonomic nervous system, and the endocrine system; it is the internal response to sensation. Arousal mobilizes the body, so that the body can more effectively deal with sensory input. RF is a group of almost 100 interconnected nuclei that are located throughout the brainstem and contains many projections into the forebrain, brainstem, cerebellum, and other structures (Iwanczuk and Guzniczak, 2015). RF is actually a complex set of networks in the core of the brainstem which mediate distinct cognitive and physiological processes (Augustine, 2016). RF has projections to the thalamus and cerebral cortex that allow it some control over which sensory signals reach the cerebrum. RF has two major neural subsystems: ascending pathways to the cortex in ARAS and descending pathways to the spinal cord in the reticulospinal tracts (Augustine, 2016). ARAS is activated non-specifically by sensory input (any type of sensory input will do). It is mostly composed of a collection of more than 20 nuclei on each side in the upper brainstem reticular core which compose several neural circuits connecting the dorsal posterior midbrain and anterior pons to the cerebral cortex via distinct pathways that project through the thalamus and hypothalamus (Figure 1, MFB-24).

Specifically, the dopaminergic ventral tegmental area and substantia nigra pars compacta, noradrenergic locus coeruleus and related nuclei, serotonergic dorsal and median raphe nuclei, histaminergic tuberomammillary nucleus, mesencephalic RF, cholinergic forebrain nucleus basalis of Meynert and pontine tegmental nuclei, glutamatergic brainstem and hypothalamic nuclei, and intralaminar and reticular thalamic nuclei make up ARAS. Neurotransmitters released by its neurons include dopamine, norepinephrine, serotonin, histamine, acetylcholine, and glutamate. These neurons exert cortical influence directly or indirectly through thalamic relays. Via these pathways, ARAS mediates arousal, attention, and consciousness. The main function of ARAS is to modify and potentiate thalamic and cortical function such that EEG

Figure 1. Medial View of the Human Brain
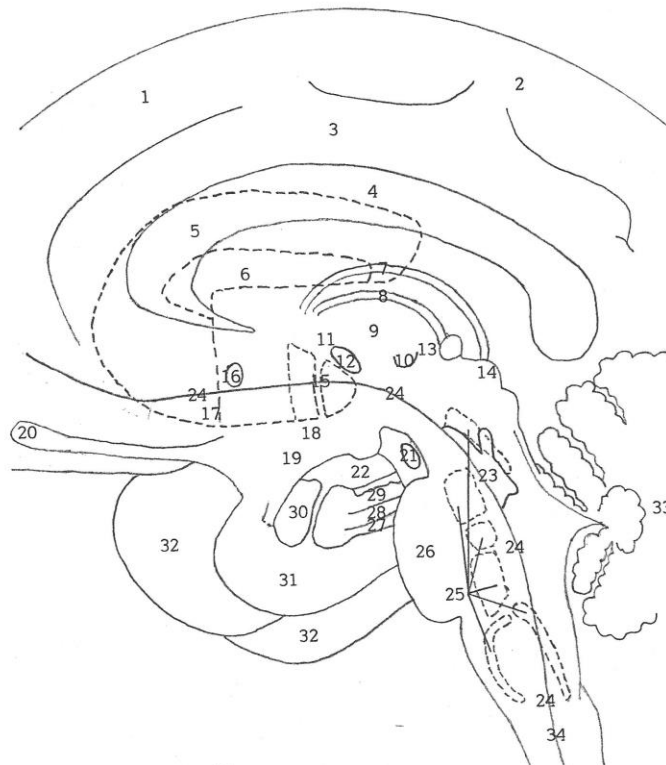
Legend:(1)Frontal Cortex, (2)Parietal Cortex, (3)Cingulate Gyrus, (4)Corpus Callosum, (5)Caudate Nucleus, (6)Putamen, (7)Fornix, (8)Stria Medullaris, (9)Thalamus, (10)Geniculate Nuclei, (11)Anterior Nucleus, (12)Subthalamic Nucleus, (13)Habenular Nucleus, (14)Superior Colliculus, (15)Globus Pallidus, (16)Septal Nuclei, (17)Nucleus Accumbens, (18)Substantia Innominata, (19Hypothalamus, (20)Olfactory Bulb, (21)Substantia Nigra, (22)Nucleus Basalis of Meynert, (23)Nucleus Coeruleus, (24)Medial Forebrain Bundle, (25)Raphe Nuclei, (26)Pons, (27)Subiculum, (28)Hippocampus, (29)Dentate Gyrus, (30)Amygdala, (31)Entorhinal Cortex, (32)Temporal Cortex, (33)Cerebellum, (34)Medulla.

desynchronization ensues. ARAS regulates wakefulness and sleep-wake transitions. The physiological change from deep sleep to wakefulness is reversible and mediated by ARAS. ARAS also helps mediate transitions from relaxed wakefulness to periods of high attention.

Extensive damage to ARAS results in coma. Partial destruction or inhibition of ARAS results in a partial loss of consciousness known as acute confusion state or delirium. The function of ARAS is modulated by its adrenergic and cholinergic components.

Attention

Attention is focussed consciousness. Attention can be voluntarily directed or reflexively drawn by sensory salience (Kincade et al., 2005). Greater activation was found in the frontal eye fields (FEF) and intraparietal sulcus, core regions of the dorsal frontoparietal attention network, demonstrating their special role in the voluntary control of attention. The right temporoparietal junction, a core region of the ventral frontoparietal attention network, was strongly modulated by stimulus-driven attentional shifts. Stimulus-driven attentional shifts recruited occipitotemporal regions and part of the dorsal network, including the FEF, suggesting a partly overlapping circuit for voluntary and stimulus-driven attention.

CONSCIOUS EXPERIENCE

Emotions

Emotions are explicit, functional, and conscious. Emotions are self-generated internal explicit states, arise rapidly in recurrent systems, take time to form, 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, can gain access to other systems, and arise from attention. Emotions are subjective ("they appear to us in a certain way", there is "something it is like" or "feels like" to have an emotion). All these properties of emotion have also been ascribed to conscious experience (Sieb, 2013).

Emotions are complex reaction patterns consisting of three components of variable intensity and prominence: a physiological component (various physiological reactions), a behavioral component (various behavioral reactions), and an experiential (conscious) component (LeDoux, 1990). The component reactions making up an emotion determine what the emotion will be recognized as. Fear, for example, may consist of increased sympathetic autonomic discharge, the release of stress hormones (epinephrine, cortisol), breakdown of energy reserves, increase in heart rate and respiratory rate, sweating, flight, cowering, freezing, fearful facial expression, fearful vocal expression, and subjective experience of fear. Happiness may consist of increased parasympathetic autonomic response, release of energy storage and conservation hormones (insulin, androgens, estrogens, oxytocin, growth hormone), storage of energy reserves, slowing of heart rate and respiration, receptive open approach behavior, smiling, happy facial expression, happy vocal expression, and subjective conscious experience of happiness. Similarly, other emotions are recognized as particular combinations of physiological, behavioral, and experiential reactions. The reactions making up an emotion can vary in kind, number, intensity, and prominence. Different emotions may share some of the same reactions. There are many varieties and degrees of emotion. It is apparent that the component reactions making up an emotion are part of arousal (activation of the autonomic nervous system, endocrine system, and ARAS), the same arousal producing consciousness.

Four analogous processes produce emotions and conscious experiences. The four processes producing emotions are: (1) sensory input, (2) identification of the emotional significance of a sensory stimulus, (3) production of an emotion, and (4) regulation of the emotion (Sieb, 2013). The four processes producing conscious experiences are: (1) sensory input, (2) identification of the conscious significance of a sensory stimulus, (3) production of a conscious experience, and (4) regulation of the conscious experience. Conscious experience and emotion both arise from sensory input. The establishment of the emotional significance of a sensory stimulus follows the establishment of the conscious significance of the sensory stimulus. The conscious significance of a sensory stimulus is established through activation of the dorsal and ventral frontoparietal attention networks. The emotional significance of a sensory stimulus is established through the rapid development of an affective valence (stimulus-reinforcement contingency) for the sensory stimulus. Humans are thought to differentiate among emotion states by interpreting sensory input associated with a generalized internal affective valence response (Zhang et al., 2019). Affective valence is developed through the relative activation of two opposing systems in the brain (Joseph, 2000; Sieb, 2013): the reward (approach) and punishment (avoidance) systems. The reward system is activated by rewarding conditioned and unconditioned stimuli, positive reinforcers, brief stimuli, low-intensity stimuli, and the cessation or absence of punishing stimuli or negative reinforcers. Base brainstem nuclei (ventral tegmental, substantia nigra, nucleus basalis, locus coeruleus, raphe) which control four major neurotransmitter systems of the brain (dopamine, acetylcholine, norepinephrine, serotonin) are part of the reward system and mediate its effects. Activation of the reward system has arousal, facilitating, rewarding, approach effects; the effects obtained through activation of the above four neurotransmitter systems. The punishment system is activated by punishing conditioned or unconditioned stimuli, negative reinforcers, long-duration stimuli, high-intensity stimuli, painful stimuli, and the cessation or absence of rewarding stimuli and positive reinforcers. The punishment system consists of a number of inhibitory limbic structures (septal nuclei, amygdala, medial hypothalamus, frontal cortex). The punishment system has arousal, inhibiting, punishing, avoidance effects. The individual works to attenuate further stimulus processing and may enter a state of quiescence and behavioral inhibition or aggression and attack. The development of affective valence begins early in sensory processing, long before sensory stimulation is recognized cognitively and consciously in the cerebral cortex. Affective valence stimulates arousal and consciousness, facilitates or inhibits stimulus processing, produces the evaluative expressive experiential aspects of emotion, and facilitates conditioned learning acquisition and expression, memory consolidation, reinforcement-expectancies for decision-making and coping responses, adaptive behavior, and social behavior (Blair, 2008; Sieb, 2013).

The amygdaloid nuclei are small almond-shaped structures found in the deep medial-temporal region of the brain, just in front of the hippocampus (Figure 1, 2). The amygdala is instrumental in the production of an emotion. The basolateral amygdaloid nuclei receive input from affective valence pathways. The central amygdaloid nuclei project to a large number of structures in the brain that are involved in the behavioral, humoral, autonomic, and experiential signs of emotions (Davis, 1991): the central grey for the arrest of ongoing behavior (freezing) or for the production of fight/flight behavior, the dorsal motor nucleus of the vagal nerve for changes in heart rate, the hypothalamus for changes in blood pressure and other autonomic

changes, the parabrachial nuclei for changes in respiration, the nucleus reticularis pontis caudalis for increased reflex excitability and for orientation and attention, the trigeminal motor nuclei for jaw movements, the facial motor nuclei for facial expressions, and the ventral tegmental area for an increase in dopaminergic, cholinergic, and noradrenergic actions in the cerebral cortex for increased vigilance, arousal, and consciousness. The amygdala is critical for the affective valence (both reward and punishment-based) needed for emotion processing. The basolateral nuclei do more than simply control the central nuclei. They enable the transmission of affective valence forward to the insula and ventromedial prefrontal cortex for emotion regulation. The posterior insula (PI) is structurally and functionally connected to sensory cortices; the anterior insula (AI) represents affective valence. From PI to AI, there is an increasing gradient of emotion activity, with an enlarged separability of emotion types (Zhang et al., 2019). Witnessing others' emotional states was shown to recruit AI.

The prefrontal cortex (PFC) is the central executive of the brain regulating specific functions carried out by other cortical and subcortical structures. PFC consists of three distinct cytoarchitectural and functional areas (John, 2009; Figure 1). The dorsolateral prefrontal cortex (DLPFC) is known as the central executive for cognitive and intentional control. It is the highest cortex for motor planning, preparation, and execution. The orbitofrontal cortex (OFC) is known as the central executive for emotion, social behavior, and decision-making. Affective valence from the amygdala is essential for its function. The ventral anterior cingulate cortex (ACC) mediates drive or motivation. Ventral ACC accesses affective valence information from the amygdala for the automatic regulation of emotion and works with OFC in the implementation of reinforcement-expectancies for decision-making. Dorsal ACC appears to be involved in the cognitive regulation of emotion. Each subdivision of PFC does not produce its functions exclusively. Each is connected through a series of subcortical structures (striatum, pallidum, substantia nigra pars reticulata, subthalamic nucleus, thalamus) back to the same PFC subdivision from which it arose. These PFC-subcortical loops have open connections with other cortical and subcortical areas. Specific neurobehavioral syndromes have been linked to preferential involvement of each of these circuits (John, 2009): the "dysexecutive syndrome", "disinhibition or pseudo-psychopathic syndrome", and "apathetic or pseudo-depressive syndrome", are linked to preferential involvement of DLPFC, OFC, or ACC circuits, respectively. These syndromes, along with the behavioral disorders associated with dysfunction of brain areas connected through open connections, bear striking resemblance to the symptom dimensions and neurocognitive dysfunctions seen in the group of conditions collectively known as schizophrenia.

Declarative (Explicit) Memory

Declarative memory is memory that can be declared (announced, made known). Study of declarative memory has provided crucial information about conscious experience, since it is the encoding, storage, and recall of conscious experience. There are two types of declarative memory: *semantic memory* has specific meaning, it is a structured record of facts, concepts, and skills; *episodic memory* is memory of personal past experiences of particular times and places with reference to the person as a participant-observer (Schacter, 2011). Episodic memory

provides basic support for semantic memory and semantic information may be derived from accumulated episodic memory.

Episodic memory derives from three core sources of information: what, where, when (Pause et al., 2013; Sieb, 2017a). Two cortical functional streams carry what, where, and when information to the medial temporal lobe of the brain for episodic memory (Eyesenck & Keane, 2010; Kandel, Schwartz, & Siegelbaum, 2021). As visual information exits the occipital lobe, it follows two main pathways. A dorsal stream leads to the parietal lobe and processes object locations in space (where) and time (when) for spatial and temporal awareness and guidance of actions. This stream begins with purely visual functions in the occipital lobe before gradually transferring to spatiotemporal awareness in the parietal lobe. The dorsal stream has strong connections to the medial temporal lobe. A ventral stream leads to the temporal lobe and is involved in representation and identification of objects (what). It has strong connections to the medial temporal lobe, limbic system, and dorsal stream. Visual information enters the ventral stream through visual area V1 and travels through V2 and V4 to the inferior temporal lobe. All parts of the ventral stream are influenced by extraretinal factors (attention, working memory, stimulus salience) in addition to the nature of the stimulus. The ventral stream not only provides a description of elements in the visual world, it also plays a role in judging their significance.

Perception is the gaining of awareness through the senses. Awareness is conscious experience of something. Perception, awareness, and conscious experience are synonymous. The critical importance of the cortical streams for conscious experience (awareness, perception) is evidenced by their disruption. Simultanagnosia is the inability to perceive or recognize multiple items, while preserving the ability to perceive or recognize single items; it is an inability to experience the visual field as a whole (Dalrymple et al., 2009; Jackson et al., 2006). The world is experienced in a patchy spotty manner, patients able to pick out a single object, or even components of an individual object, without being able to see the global picture. In dorsal simultanagnosia, damage occurs to the occipital-parietal junction (dorsal stream); perception is limited to single objects. In ventral simultanagnosia, damage occurs to the left inferior occipital-temporal junction (ventral stream); patients can perceive several objects, but can only recognize one at a time. Balint syndrome is a triad of simultanagnosia, oculomotor apraxia (difficulty in fixating the eyes), and optic ataxia (inability to move the hand to a specific object by vision). Parietal lobe damage impacts visuospatial skills, visual scanning, attention, conscious experience, and cognitive function (Kandel, Schwartz, & Siegelbaum, 2021). Left (dominant) parietal lobe damage causes dysphasia/aphasia, dyscalculia, dyslexia (difficulty in interpreting words, letters, symbols), apraxia (inability to perform complex movements in the presence of normal motor, sensory, and cerebellar function), agnosia (inability to recognize or discriminate), and Gerstmann syndrome (acalculia, agraphia, finger agnosia, difficulty in right-left differentiation). Right (nondominant) parietal lobe lesions result in loss of imagery, loss of visualization of spatial relationships, neglect of left side of space and left side of the body, spatial disorientation, akinetopsia (inability to perceive motion), constructional apraxia, dressing apraxia, anosognosia (unaware of disability), and drawings may be neglected on the left side. Amorphsynthesis is a loss of awareness of one side of the body caused by a lesion in a parietal lobe. Usually, left-sided lesions cause agnosia and a full-body loss of awareness; right-sided lesions cause lack of recognition of the person's left side and left extra-personal space.

The encoding, storage, and recall of conscious experience (episodic memory) depends on the hippocampus and surrounding structures of the medial temporal lobe. Lesions that include the

hippocampus (dentate gyrus-DG, CA fields, subiculum-SUB), amygdala, parahippocampal region (entorhinal cortex-EC, perirhinal cortex-PER, parahippocampal cortex-PHC), retrosplenial cortex (RSC), and insular cortex (IC) impair episodic memory in humans (Manns & Buffalo, 2013; Figure 1, 2). The name entorhinal (inside rhinal) derives from the fact that EC is partially enclosed by the rhinal (olfactory) sulcus. EC lies immediately adjacent and ventral to PER and PHC. RSC lies immediately behind the splenium of the corpus collosum. IC lies deep inside the sylvian fissure beneath the junction (operculum) of the parietal, occipital, and temporal lobes. The parahippocampal region (EC, PER, PHC) serves as a convergence site for input from neocortical areas into the hippocampus and redistributes projections from the hippocampus back into the neocortex. Working in concert with the hippocampus, the parahippocampal region plays

Figure 2. The Hippocampus and Adjacent Structures of the Medial Temporal Lobe
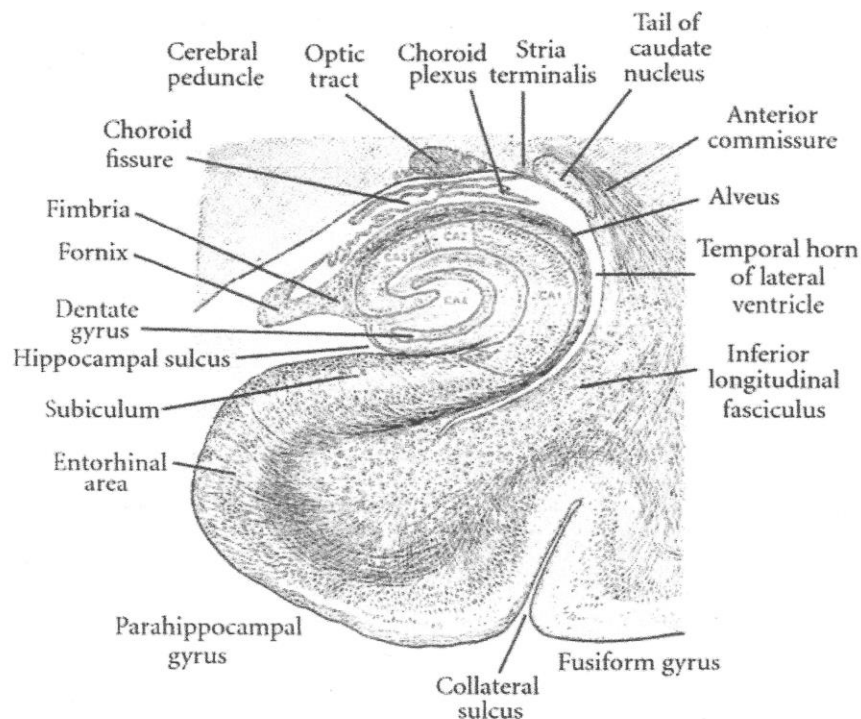
an essential role in episodic memory (Furtak & Brown, 2018). The parahippocampal region supplies the hippocampus with what, where, and when information from the dorsal and ventral cortical streams. PER receives mainly inputs from neocortical areas important for nonspatial information (the ventral stream) and unitizes stimulus characteristics into a single representation of what. PHC mainly receives inputs from cortical areas important for allocentric spatial (where) and temporal (when) information (the dorsal stream). PHC is dominated by visuospatial inputs from posterior parietal cortex. PHC codes for specific navigational landmarks and some PHC cells have place fields that are larger and more sensitive to environmental cues than hippocampal place cells. RSC provides a strong projection to PHC. RSC has dense reciprocal connections with visual cortex, dorsal presubiculum, anterior thalamic nuclei, and hippocampus. RSC contains head direction cells, speed cells, conjunctive cells (reflect more than one parameter at once), and cells with weak spatial coding. RSC is implicated in a wide range of cognitive functions including *episodic memory, spatial navigation, imagining future events, and*

processing scenes (Ritchey et al., 2015). RSC is particularly responsive to permanent non-moving environmental landmarks and in using them to make spatial judgements. When damaged, RSC produces both anterograde and retrograde amnesia. Lesions of RSC may display a form of topographical disorientation where people can recognize and identify environmental landmarks, but are unable to use them to orientate themselves. The PHC-RSC system has been linked to memory for spatial and temporal information and in discriminating novel and familiar *object-context configurations* (Ritchey et al., 2015). The PHC-RSC system plays a key role in spatial navigation. The coordinated actions of components of the PHC-RSC system integrate information about *one's position within a global spatiotemporal context to construct a first-person topographical representation* (Ritchey et al., 2015). EC is subdivided into lateral (LEC) and medial (MEC) subdivisions which are characterized by largely different input-output connectivity (Manns & Eichenbaum, 2007). LEC receives more projections from PER. MEC receives more projections from PHC. What information reaching PER follows a path through LEC to the hippocampus that parallels the path followed by when and where information from PHC through MEC to the hippocampus. These pathways are largely combined in DG and CA3, but kept at least somewhat separate in CA1 and SUB. Parallel functionally-distinct input streams to the hippocampus are tempered by the presence of a substantial projection from PHC to PER (and a smaller return projection) and connections between LEC and MEC. The connectivity of EC shows strong topographical organization along a gradient that runs from its border with the rhinal sulcus towards its border with the hippocampus (Witter, 2011). Multimodal sensory cortex providing inputs representing the outside world preferentially targets a strip of EC which is adjacent to the rhinal sulcus, including portions of both the lateral and medial divisions. Parts of the two divisions that are more distant from the rhinal sulcus receive different information (olfactory, amygdaloid). Output of EC to the hippocampus is mapped with a topographical organization as well, such that the zone of EC closest to the rhinal fissure preferentially connects with the dorsal (posterior) part of the hippocampus, whereas portions of EC positioned more distant from the rhinal fissure connect more to the ventral (anterior) part of the hippocampus. Input to the hippocampus mainly comes from superficial layers II and III of EC; output of the hippocampus preferentially targets deeper layers V and VI of EC. Layers V and VI are the origin of widespread cortical projections and subcortical projections to the septum, striatum, amygdala, and thalamus. Reciprocal interactions between deep and superficial layers of EC are quite substantial. EC, in conjunction with the hippocampus, deals with the translation of neocortical exteroceptive information into conscious experience.

Within the hippocampus, an intricate pattern of connectivity mediates the rapid encoding of novel conjunctions of information. There are four histological subdivisions of the hippocampus: CA1, CA2, CA3, and CA4 (Figure 2, 3). The main output of EC comes from the large stellate pyramidal cells in layer II that "perforate" SUB and project densely to the granule cells of DG, less densely to the apical dendrites of CA3, and sparsely to the apical dendrites of CA1 (Kandel, Schwartz, & Siegelbaum, 2021; Purves, 2011). This path establishes EC as the main interface between the hippocampus and other parts of the cerebral cortex. Information flow from EC through the hippocampus is largely unidirectional, with signals propagating through a series of tightly packed cell layers, first to DG, then to CA3, then to CA1, then to SUB, and then out of the hippocampus to EC (Jiang et al., 2019; Figure 2, 3). Each of these layers also contains complex intrinsic circuitry and extensive longitudinal connections. Within the hippocampus, DG granule cell axons pass on information to the proximal apical dendrites of CA3 pyramidal cells; 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 EC; CA1 also sends axons back to EC, but these are more sparce than the CA3 projection. Besides output to EC,

Figure 3. The Internal Structure of the Hippocampus
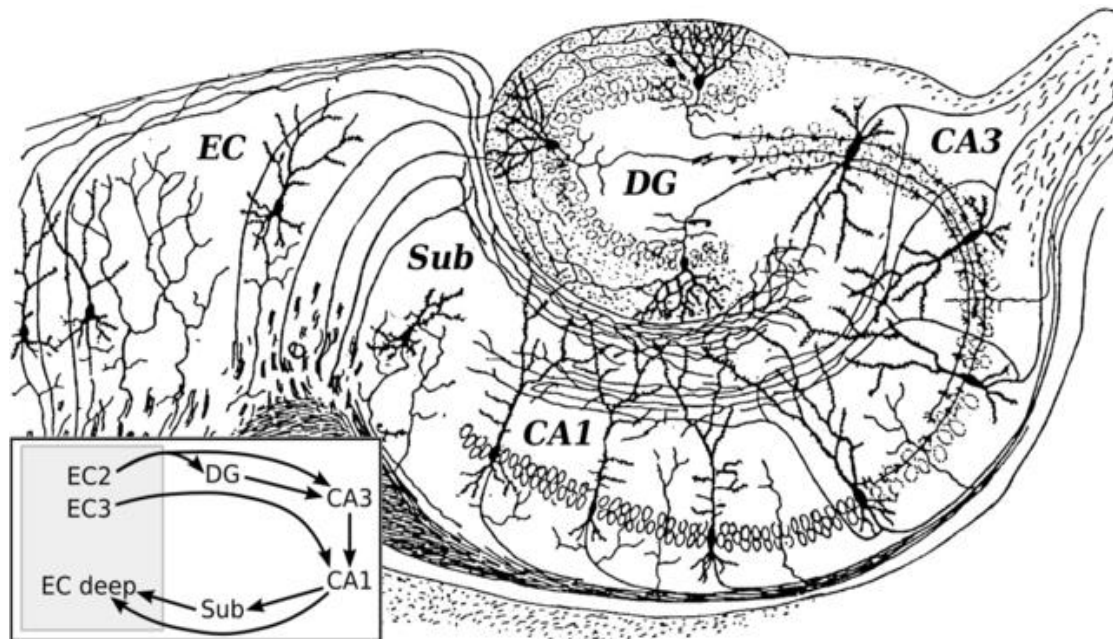
additional output goes to PER, PHC, PFC, lateral septal area, and mammillary body. CA1 receives modulatory input from the serotonin, norepinephrine, and dopamine systems. A very important projection comes from the medial septal area, which sends cholinergic and GABAergic fibers to all parts of the hippocampus. The septal area plays 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.

The outcomes of hippocampal processing are directed back to adjacent parahippocampal areas. The outputs of that region are directed in turn back to the same neocortical areas that were the source of its inputs. All parts of the neocortex are topographically represented in the hippocampus in a compressed manner and all are addressed by hippocampal output (Buzsaki, 2011). Insights about the global function of the hippocampus depend on the portion of the hippocampus investigated (Buzsaki, 2011). Studying the physiological pattern of the dorsal (non-primates) posterior (primates) hippocampus in animals gave rise to the cognitive map theory for hippocampal function. Studying the surgical removal of the uncus and body of the hippocampus in human drug-treatment resistant cases of epilepsy, lead to the conclusion that the hippocampus is responsible for episodic memories. These conceptual differences should be viewed as arising from the same mechanisms, but from study of different parts of the hippocampus (Buzsaki, 2011).

Because of its densely packed neural layers, the hippocampus generates some of the largest EEG signals of any brain structure. Three major EEG patterns characterize the temporal dynamics of the hippocampal system: theta oscillations (4-10 Hz), sharp waves and associated ripples (140-200 Hz), and gamma (30-130 Hz) oscillations. These patterns define the

physiological state of the hippocampus (Buzsaki, 2006). The hippocampus has two major modes of activity named after the EEG patterns associated. The theta-gamma mode is associated with exploratory movement and REM sleep, while intermittent sharp waves mark immobility, consummatory behaviors, and slow-wave sleep. These two competing states also largely determine the main direction of information flow, with neocortical-hippocampal transfer taking place mainly during theta-gamma and hippocampal-neocortical transfer during sharp waves. Switching between states is largely determined by subcortical neuro-modulatory inputs. The theta-gamma mode appears during states of active alert behavior and 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), hippocampal theta appears. At these times, the EEG of the hippocampus is dominated by large regular waves at 3-9 Hz, often continuing for many seconds. The main groups of neurons 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. As behavior occurs, 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 (place) of the animal, but other behavioral variables also clearly influence it. The large irregular activity mode of the hippocampus appears during slow-wave sleep and also during states of waking immobility, such as resting or eating. During sleep or waking states, when people are resting or otherwise not engaged with their 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* (SPWs). SPWs (randomly-timed large deflections of the EEG signal) dominate the EEG. They are frequently generated in sets containing up to 5 or more individual SPWs. The spiking activity of neurons within the hippocampus is highly correlated with SPW activity. Most neurons decrease their firing rate between SPWs; however, during SPWs, there is a dramatic increase of firing rate in up to 10% of the hippocampal population. These events are associated with short-lived high-frequency EEG oscillations called "ripples". SPWs are most frequent during sleep. They are less frequent during inactive waking states and are usually smaller. SPWs have been observed in humans. One of the most interesting aspects of SPWs is that they appear to be associated with memory. 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*, occurs mainly during SPWs. Buzsáki (2011) and others propose that memories are stored within the hippocampus during behavior and then later transferred to the neocortex during sleep. SPWs are suggested to drive synaptic changes in the neocortical targets of hippocampal output pathways. It has been hypothesized that the theta/SPW switch supports a two-state memory mechanism with a rapid acquisition stage during theta-gamma, followed by repeated reactivation during post-experience SPWs (Buzsaki, 2011). SPWs are characterized by a three to five-fold gain of network excitability, creating short time windows for efficient transfer of hippocampal information to the neocortex. Both place cell sequences and the distances between place fields are reflected by SPWs, and their selective elimination after learning interferes with memory

consolidation. Because of the hippocampus, newly acquired memories are gradually transferred to neocortical stores. The hippocampus ceases to play a role in the retention of episodic memory after a period of time. The hippocampus also allows a fast and efficient search among memories deposited in the neocortex (Buzsaki, 2011).

Long Term Potentiation

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 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 strength induced by brief strong stimulation that lasted for hours to days or longer. This phenomenon was referred to as long-term potentiation (LTP). As a 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. The best-studied form of LTP occurs at synapses that terminate on dendritic spines and use the neurotransmitter glutamate. Several major pathways within the hippocampus fit this description and exhibit LTP. 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 (Shouval, Wang & Wittenberg, 2010). LTP occurs because of the increased Ca^{++} release in the active synapses. This is complemented by the synthesis of new neurons in DG (Abbott & Nigussie, 2020).

Representation of Space in the Hippocampus

A fundamental feature of episodic memory (and of conscious experience) is the spatial distribution of events. In 1971, John O'Keefe discovered *"place cells"* in the hippocampus. He found that place cells fire at particular places in a spatially-structured environment as a test animal moves around the environment. Place cells fire so reliably one can tell where the animal is in an environment by observing which neurons are firing. A place cell fires when the animal passes through a specific small region of space called the place field. Place fields are considered allocentric rather than egocentric because they are defined with respect to the outside world, rather than the body. By orientation based on the environment, place cells can work effectively as neural maps of the environment. This led to a series of investigations that culminated in a book entitled *"The Hippocampus as a Cognitive Map"* by O'Keefe and Nadel in 1978 which argued that the hippocampal neural network instantiates cognitive maps for spatial memory function. This motivated hundreds of experimental studies aimed at clarifying the role of the hippocampus in spatial memory, spatial navigation, spatial learning, and awareness (conscious experience): impairments of spatial learning and awareness were found after damage to the hippocampus and place cells within; without a fully functional hippocampus, humans may not remember where they have been or how to get where they are going; an intact hippocampus is required for initial learning and retention in some spatial memory tasks; people have more active hippocampi when correctly navigating; the hippocampus plays a role in finding shortcuts and

new routes between familiar places; and the hippocampus has been found to be larger in taxi drivers than in the general public (Sieb, 2016, 2017b).

Many hippocampus neurons have place fields and fire bursts of action potentials in the gamma range when a freely-moving animal passes through particular places in the environment. A place cell has only one, or a few, place fields in a typical small laboratory environment, but more in a larger environment. Place cells fired in different areas of the hippocampus depending on where the subject went; there is no apparent topography of place fields, with neighboring place cells as likely to have distant fields as close fields. This whole firing network made up the subject's environment. 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. Place cell firing is stabilized to resist small changes in sensory input, but responds collectively and coherently to large changes.

Place cell responses are shown by pyramidal cells in the hippocampus proper (CA fields) and granule cells in DG. 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 almost silent when a subject is moving outside of the place fields, but reach sustained rates in the gamma range when the subject is near the center. Neural activity sampled from 30 to 40 randomly chosen place cells carries enough information to allow a subject's location in an environment to be reconstructed with high confidence.

Place cells fire more rapidly when a new item was added to the environment, or when an item that is usually there is not present. In some cases, the firing rate depends on the direction the subject is moving, the destination toward which the subject is traveling, and other task-related variables. As environments changed, the same place cells would fire, but the relationship and dynamic between firing fields would change. As subjects 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. There are both simple place cells with purely location correlates and complex place cells that increase their firing rate for a particular object. Others fire when expectations in a particular location are not met or when novelty is encountered.

In 2014, John O'Keefe, May-Britt Moser, and Edvard Moser were awarded the Nobel Prize in Physiology or Medicine for the discovery of "*grid cells*", cells that constitute a *"positioning system"* in the brain. Grid cells help animals understand their position in space. Grid cells have been identified in rats, bats, monkeys, and humans. A grid cell fires when a freely-moving animal traverses a set of small regions (firing fields) roughly equal in size and arranged in a periodic triangular array (grid) that covers the entire available environment (Hafting et al., 2005; Figure 4). Firing fields are equally spaced apart, such that the distance from one firing field to all six adjacent firing fields is approximately the same. Doeller and coworkers (2010) provided the first evidence for grid cell like representations in humans that implicates a network of regions supporting spatial cognition and autobiographical (episodic) memory. *This network consisted of the entorhinal/hippocampal/subicular, posterior and medial parietal, lateral temporal, and medial prefrontal cortical areas.* The signal was greatest in right EC. Doeller concluded: "grid

Figure 4: A Hexagonal Lattice. The dots are firing fields of a grid cell.
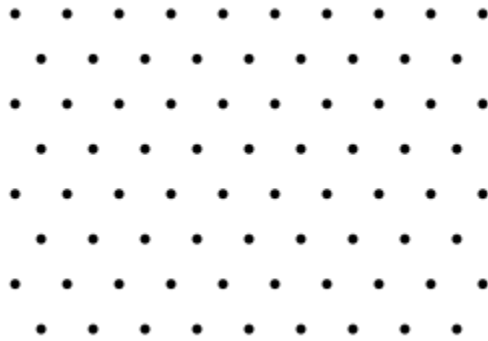
cells provide a strikingly periodic representation which is suggestive of very specific computational mechanisms". The regularity in grid spacing does not derive from any regularity in the environment or in the sensory input available. Grid cells encode an abstract structure inside the brain which is imposed on the environment with no regard for the sensory features of the environment. Grid patterns appear on the first entrance of a subject into a novel environment and usually remain stable thereafter. When the subject enters a completely different environment, grid cells maintain their grid spacing and the grids of neighboring cells maintain their relative offsets.

Place-specific firing persisted in CA1 neurons even after removal of all intrahippocampal input from CA3 (Witter, 2011). Because only direct inputs from EC were left by these lesions, it was concluded that place-specific signals were computed upstream of the hippocampus. Principle cells in layers II and III of the area of MEC that provided the strongest input to place cells of the dorsal hippocampus had multiple sharply-tuned firing fields which collectively signalled the animal's changing position with a precision similar to that of place cells in the hippocampus. When these cells were recorded in sufficiently large environments, it became clear that the many firing fields of each neuron formed a periodic triangular array, or grid, that tiled the entirety of the animal's environment. Grid cells in layers III and V of EC intermingle with cells that code for the direction the animal is moving (head-direction cells), cells with grid and head-direction properties (conjunctive cells), speed cells (track the speed of the animal), and boundary cells (Moser, 2019; Witter, 2011). How is the periodic firing pattern of grid cells transformed to the non-periodic signal of place cells? If grid inputs to place cells vary in spacing and orientation, linear summation would result in the experience of only a single large field. Since a location in the hippocampus receives inputs from more that 25% of the axis of MEC, this appears to be the most likely scenario (Buzsaki, 2011).

Representation of Time in the Hippocampus

Another fundamental feature of episodic memory (and of conscious experience) is the serial organization of events. Studies on humans have shown that the hippocampus is critical to remembering the flow of events in distinct experiences, and in doing so, bridges temporal gaps between events (MacDonald et al., 2011). There is a robust hippocampal representation of sequence memories, highlighted by "time cells", cells that encode preferred and consistent temporal gaps between key events, while also encoding location and ongoing behavior. The

hippocampus is essential for encoding and remembering unique sequences of events as well as disambiguating sequences that share common events.

Time cells offer a specific mechanism for the representation of temporal information in episodic memory. Representation of temporal information is critical for both the encoding and retrieval of episodic memories. Umbach and coworkers (2020) identified populations of single pyramidal neurons in the hippocampus during memory encoding and retrieval in which temporal location consistently modulated spiking activity. Time cell activity predicted the temporal organization of retrieved memories and the stability of the time signals during encoding influenced the ability to temporally order memories at the time of retrieval. With properties shared with place cells, time cells offer a unifying physiological mechanism for the representation of temporal information in the hippocampus (Umbach et al., 2020).

Complementing the identification of time cells, a distinct population of "ramping cells" whose activity gradually rises or decays across behavioral epochs was found in EC of humans (Umbach et al., 2020). Ramping activity was demonstrated across behavioral epochs of various lengths and reliably mapped out the temporal dimensions of a given task, a crucial feature in real-world episodic memory. This is similar to grid cells which reliably map out the spatial dimensions of a given task. Ramping cells provide information at longer time scales than hippocampal time cells. Ramping cells are sensitive to contextual changes and could represent the slowly evolving nature of contextual information. EC is rich in neurons that demonstrate ramping activity across multiple timescales simultaneously. Ramping cells may serve as a link between temporal context and hippocampal time cells (Umbach et al., 2020). Similarly, grid cells may serve as a link between spatial context and hippocampal place cells.

Representation of Space and Time in the Hippocampus

Episodic memory describes our ability to weave events into rich and coherent experiences. Event (what) information is precisely linked to temporal (when) and spatial (where) information to create complex and coherent experiences. Time cells and place cells map to specific memory events, are specific to task context, and link to successful episodic memory. The hippocampal representation of time is quite similar to its representation of space (MacDonald et al., 2011; Umbach et al., 2020): a large proportion of neurons are engaged in both; time cells reliably fire at preferred and consistent moments, or time fields, much as place cells reliably fire at preferred and consistent locations, or place fields; time cells signal the nature and timing of salient events, place cells signal the nature and spatial location of salient events; time cells disambiguate overlapping sequence memories, place cells disambiguate overlapping routes; time cells partially "retime" when key temporal parameters are altered, place cells partially "remap" when critical spatial cues are altered; time cells work in conjunction with ramping cells, place cells work in conjunction with grid cells; variability in place cell and time cell firing reflects the representation of event features beyond spatial and temporal representation respectively. Hippocampal neuronal ensembles segment temporally-organized memories much as they segment spatially-organized memories. Both time cells and place cells exhibit theta phase precession and LTP. Place cells and time cells offer a unifying mechanism for the representation of spatial and temporal information in the hippocampus. MacDonald and coworkers (2011) conclude: "place

cells and time cells reflect fundamental mechanisms by which hippocampal neural networks parse any spatiotemporal context into quantal units of where and when important events occur, bridging, and thereby organizing events, in a conceptual organization of events." Eichenbaum (2014) concludes: "the firing properties of time cells parallel the properties of place cells and provide an additional dimension that is integrated with the spatial dimensions." Both investigators conclude: "hippocampal neurons differentially encode key events in space and time and compose unique spatiotemporally-organized representations of specific experiences."

Space-Time Intervals

A space-time interval (s) is the distance between two events in space and time. *The square of a space-time interval (s^2) is given by the square of the difference of the space coordinates of two events minus the square of the difference of the time coordinates of the events:*

$s^2 = (x_1-x_2)^2 + (y_1-y_2)^2 + (z_1-z_2)^2 - (ct_1-ct_2)^2$ or $s^2 = \Delta r^2 - c^2\Delta t^2$,

where c is the speed of light, r^2 is $(x_1-x_2)^2 + (y_1-y_2)^2 + (z_1-z_2)^2$, ct is time (the distance light travels), s is the space-time interval, while s^2 is often taken as the space-time interval to avoid square roots and negative values. By this formulation, space-time intervals are invariant; they are the same (invariant) regardless of the coordinates used in their representation (Einstein, 2001; Petkov, 2010; Susskind, 2012). When s^2 is zero, the interval is light-like. When s^2 is negative, the interval is time-like. When s^2 is positive, the interval is space-like.

Light-Like Space-Time Intervals

When the difference in the space coordinates of two events is exactly equal to the difference in the time coordinates of the events ($\Delta r^2 = c^2\Delta t^2$), the space-time interval is zero ($s^2=0$) and called a light-like space-time interval. The spatial distance between the two events is equal to the distance light travels (the time) between the events. Light-like space-time intervals determine the nature of conscious events through the conveyance of defining information about the events to the eyes ("what"). Light-like space-time intervals may be considered fundamental to the organization of human conscious experience, since they are a basic part of the organization of all conscious experiences (see introduction).

Time-Like Space-Time Intervals

If the difference in the time coordinates of two events is greater than the difference in the space coordinates of the events ($c^2\Delta t^2 > \Delta r^2$), s^2 is negative ($s^2<0$) and called a time-like space-time interval. Because signals and other causal influences cannot travel faster than c, time-like intervals define the concept of causality. Since for time-like intervals, signals or information can travel between the events at less than c, one event can influence or be influenced by the other event. One event could be the cause or effect of the other event. If B causes A, B exists in the past relative to A. If B is caused by A, B exists in the future relative to A. Events with time-like separation may be said to have a past or future relation. A reference frame exists where events may be separated only by time, but not by space; these events may occur at the same spatial location, but at different times. Time-like space-time intervals account for the experience of conscious events at the same spatial locations, but at different times (this can occur only with time-like separation of the events). This can be observed in human conscious experience (see introduction). Conscious events which occur at the same spatial location, but at different times

(time-like separation), often have a cause-effect relationship and necessarily a past-future relationship. Time-like space-time intervals carry the "when" information for the organization of human conscious experience. Time-like space-time intervals may be considered fundamental to the organization of human conscious experience, since they are a basic part of the organization of all human conscious experiences. Time cells represent time-like separations.

Space-Like Space-Time Intervals

If the difference in the space coordinates of two events is greater than the difference in the time coordinates of the events ($\Delta r^2 > c^2 \Delta t^2$), s^2 is positive ($s^2 > 0$) and called a space-like space-time interval. One event cannot affect the other event because signals or information would have to travel between them faster than c. There exists a reference frame where events may be separated only by space, but not by time; such events may occur simultaneously, but at different spatial locations. Space-like space-time intervals account for the experience of conscious events simultaneously, but at different spatial locations (this can occur only with space-like separation of the events). This can be observed in human conscious experience (see introduction). Generally, the events do not to have cause-effect or past-future relations. Space-like space-time intervals carry the "where" information for the creation of human conscious experience. Space-like space-time intervals appear to be fundamental to the organization of human conscious experience, since they are a basic part of the organization of all conscious experiences. Place cells represent space-like separations of events.

Neuronal oscillations

Neuronal oscillations are rhythmic fluctuations in neuronal firing. Gamma oscillations (25 – 130 Hz) are prominent across multiple brain regions, including the hippocampus. Fast gamma (55+ Hz) in the hippocampus is coupled with fast gamma from MEC, an area that processes current sensory information and is the main input to the hippocampus. Fast gamma has been proposed for the transmission of current sensory information to the hippocampus during new memory encoding (Mably & Colgin, 2018). Hippocampal fast gamma dominates during exploration of novel objects and places and hippocampal place cells represent locations and current trajectories during periods of fast gamma; slow gamma (25-50 Hz) was coupled with memory retrieval. Theta oscillations are a prominent 4-10 Hz rhythm in the hippocampus of all mammals studied, including humans. Theta is essential for the normal functioning of the hippocampus because manipulations that disrupt it produce behavioral impairments that mimic hippocampal lesions (Lubenov & Siapas, 2009). The rich consortium of theta generators in the hippocampus and parahippocampal regions were coordinated by the medial septum and a network of long-range interneurons. Theta and gamma oscillations co-exist in the hippocampus and couple to control communication and function between regions (Jiang et al., 2019).

Theta Phase Precession

Theta phase precession is a neurophysiological process in which the firing of action potentials by individual neurons is timed to the phase of theta oscillation of the local population of cells. In the hippocampus, activity of individual place cells is modulated by position and by a slower population theta oscillation (Lubenov & Siapas, 2009). As the subject moves, individual place cells fire action potentials at an increased rate at particular places along the path called

place fields. Each place cell's maximum firing rate (in the gamma range) occurs at the center of the particular place field encoded by that cell. Although simple rate coding (the coding of information based on whether neurons fire more rapidly or more slowly) may account for some of the neural coding of place, there is also a prominent role for the timing of the action potentials of a single place cell, relative to the theta oscillation. The firing of the local population of cells is organized to occur synchronously forming wavelike theta voltage oscillations that is measurable as the local field potential. Although the occasional action potentials of cells outside of place fields occur in phase with (at the peaks of) the theta waves, the bursts of more rapid spikes elicited when subjects reached place fields were out of synchrony with the theta. As the subject entered a place field, the corresponding place cell would fire slightly in advance of the theta oscillation wave peak. As the subject moved closer and closer to the center of the place field, successive action potentials occurred earlier and earlier within the theta wave cycle. At the center of the place field, when the cell would fire at its maximal rate, firing had advanced sufficiently to be anti-phase to the theta oscillation (at the bottom or trough, rather than the peak, of the theta wave-form). As the subject continued to move on past the place field center and the cell firing slowed, the action potentials continued to occur progressively earlier relative to the theta wave, until they again became synchronous with the wave, aligned now with one wave peak earlier than before. This advancement of firing relative to the theta wave is called theta phase precession. Subsequent studies showed that each time a subject entered a completely different area and the place fields remapped, place cells would again become phase-locked to the theta oscillation. This has been established experimentally and it is now widely accepted that theta phase precession is an important component of information coding about place (Lubenov & Siapas, 2009). Hippocampal time cells also exhibit significant theta-phase precession during new memory encoding (Umbach et al., 2020). Time cell firing advanced to earlier phases of the theta cycle and peak firing occurred near the trough of the theta cycle. As firing rate slowed from local maxima, phase precession continued. Theta phase precession gates synaptic plasticity because the timing of firing with respect to the phase of theta is important in determining the magnitude and direction of synaptic change (Lubenov & Siapas, 2009).

Theta phase precession unifies the encoding of space and time in the hippocampus during new memory encoding (Umbach et al., 2020). The duration of the theta cycle sets a natural upper limit to space and time encoding and the number of gamma cycles/theta determines spatial and temporal resolution (Buzsaki, 2011). The mechanism limits attention and memory capacity. Episodic recall is high for conditions that surround a recalled event, whereas conditions representing the far past or far future are less resolved (Buzsaki, 2011). However, as recall moves forward in time, subsequent events gain high contextual resolution. Not only adjacent, but more distant assemblies may be linked, providing for higher-order associations.

Travelling Waves

Lubenov and Siapas (2009) found that theta oscillations had a progressive gradient of phase offsets along the length of the hippocampus. They could only explain this by characterizing theta oscillations as travelling waves with consistent speeds and directions. They found that whenever robust theta oscillations are present in the hippocampus, they appear as travelling

waves. Travelling waves ensure that the instantaneous output of the hippocampus consists of topographically-organized segments of space and time of characteristic length (Lubenov & Siapas, 2009), space-time intervals.

Cognition

Studies indicate that the dorsal and ventral cortical streams carry what, where, and when information to the medial temporal lobe and that the prefrontal cortex extracts space-time intervals from the hippocampus for cognition. Both posterior parietal cortex (PPC) and PFC have been implicated in time-experiencing (Wendelken, 2015): the cerebellum, right PPC, right PFC, frontal-striatal circuits, and IC for *duration perception*; the inferior frontal and superior temporal lobes, hippocampus, medial PFC, medial parietal, and posterior cingulate cortex for *past–future distinction and mental time travel*; the PFC, inferior parietal cortex, superior colliculus, and IC for *synchronous and asynchronous event distinction*; and posterior sylvian regions, PPC, and temporo-parietal networks for *temporal order judgment*. This large-scale meta-analysis indicated clearly that a key function of PPC is visuospatial attention and spatial and temporal processing in general. Lara and Wallis (2015) found that the strongest activity of the overwhelming majority of PFC neurons reflect the spatial location of stimuli and the passage of time. Various lines of research suggest a strong, but flexible, connection between spatial and temporal cognition in PPC and PFC (Wendelken, 2015). Reasoning is among the most complex of cognitive processes. Wendelken (2015) observed stronger PPC activation for reasoning with inequalities, than for reasoning with equalities, and argued that this was due to representation of the more specific inequality relationships. This is interesting as space-like and time-like space-time intervals are inequalities. Wendelken (2015) concluded: "the extraction of mental relations (space-time intervals?) from the hippocampus initiates an important process of relational integration." He found that the rostrolateral PFC extracts mental relations from the hippocampus and is specialized for second-order relational reasoning. He also found that current evidence points away from logical rule-following as a primary mechanism for reasoning and is more consistent with accounts that involve estimation and probabilistic computation.

Causal inference is a fundamental component of *cognition and perception*, binding together conceptual categories, *imposing structures on perceived events*, and guiding decision-making (Cummins, 2014). Neuro-imaging shows that the brain distinguishes causal events from non-causal events (Cummins, 2014). There are significantly higher relative levels of activation in the right middle frontal gyrus and right IPC for causal relative to non-causal events. Causal judgments generated distinct activation in left dorsolateral PFC and right precuneus (part of the superior parietal lobule), substantiating the particular involvement of these areas in assessments of causality. Perceptual causality can be distinguished from inferential causality. Inferential causality (a causal relationship determined by evidence and reasoning) activates the medial frontal cortex, with particular left hemispheric involvement. Perceptual causality (causal relationships determined by observation) activates the right parietal lobe suggesting that the right parietal lobe is involved in the processing of the spatial and temporal attributes of causality.

Working memory describes a process of short-term storage of information to support ongoing or upcoming action and is considered a crucial component of the executive control of

goal-directed behavior (Mansouri et al., 2015). The retention of task-relevant information is essential for complex behaviors which evolve in space and time, in order to maintain perception and behaviors in a coherent and goal-directed framework. Working memory is crucial for the temporal organization of behavior, linking processes across delays. In recent years there has been a steady stream of novel research that has challenged the widely held view that PFC stores task relevant information in working memory. Lara and Wallis (2015) found that sensory information is maintained in working memory by the same posterior sensory neurons that represent that information in the sensory environment (parietal cortex) and that the overwhelming majority of PFC neurons failed to encode working memory; instead, the strongest PFC signals reflected the passage of time and the spatial location of stimuli. Both of these signals play an important role in the performance of a task, but do not reflect the contents of working memory. They do, however, support the contention that space-time intervals are extracted from the hippocampus by the PFC for cognitive function.

Goyal et al. (2020) identified multiple patterns of theta-band oscillations along the length of the human hippocampus. High theta oscillations (~8 Hz), which varied with the speed of movement, were found mainly in the posterior hippocampus and appeared to be particularly important for spatial processing. Low theta (~3-4 Hz) was more often found in the anterior hippocampus and linked to memory processing. The posterior-to-anterior fast-to-slow theta oscillatory gradient that was observed in the hippocampus seems to match the direction of the oscillatory gradient found in the neocortex (Goyal et al., 2020). There could be a functional link between alpha rhythms in the posterior neocortex and high-theta oscillations in the posterior hippocampus and between frontal-midline (Fm) theta oscillations and low-theta oscillations in the anterior hippocampus. The correlation between high-theta frequency and movement speed suggests that this oscillation could relate to the kinds of visuospatial processes that are commonly associated with occipital alpha oscillations. Fm theta oscillations are of particular interest in regard to higher cognitive functions (Enriquez-Geppert et al., 2014). Fm-theta oscillations are recorded over frontal-medial brain regions and appear to be generated in the mid-cingulate cortex (MCC), a highly interconnected brain structure, that is part of the superordinate cognitive control network. MCC is known to be crucially involved in executive functioning, which enables goal-directed behavior. Enhanced cognitive processing is accompanied with increases of Fm-theta, specifically in tasks involving working memory and executive functions. Fm-theta activity has been related to efficient working memory maintenance and increases of Fm-theta during task processing predicts successful behavioral performance and conflict monitoring. The finding that different theta frequencies are preferentially associated with anterior and posterior processes is notable given the predominant involvement of the frontal and occipital lobes in high-level processing and sensory processing, respectively. Along with the different functional correlations found for low and high-theta frequencies, these results are consistent with the idea that oscillations at varying frequencies reflect distinct hippocampal-neocortical interactions related to different functions. This multiplicity of human theta patterns across high and low frequencies could be a critical component in allowing the human hippocampus to coordinate a diverse set of brain-wide neural assemblies to support various types of behavior. Oscillation of distant neural structures can synchronize to form large-scale oscillating networks. Neural oscillations may coordinate neuronal spiking between and within brain circuits and coherent large-scale brain activity may form dynamic links between brain

areas required for the distribution and integration of information. Neural oscillation and synchronization have been linked to many cognitive functions such as *information transfer, perception (conscious experience), memory, and motor control* (Enriquez-Geppert et al., 2014; Lara and Wallis, 2015). Hippocampal damage inhibits behavioral responsiveness, shifts in attention, spatial navigation, habituation, divergent thinking and response, 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.

CONCLUSION

Consciousness is an active, causal, and functional part of brain processing. Arousal (activation of the autonomic nervous system, endocrine system, and ARAS) by sensory input produces the awake (conscious) state. The dorsal and ventral frontoparietal attention networks are activated defining the conscious significance of sensory input. What, where, and when information is conveyed by the dorsal and ventral cortical functional streams to the medial temporal lobe for the encoding, storage, and recall of conscious experience (episodic memory). Hippocampal place cells and time cells encode events in space and time within spatiotemporal contexts provided by entorhinal cortex grid cells and ramping cells. Theta phase precession unifies the encoding of space and time in the hippocampus. Theta travelling waves ensure that the instantaneous output of the hippocampus consists of topographically-organized segments of space and time (space-time intervals). Place cells and time cells reflect fundamental mechanisms by which hippocampal neural networks parse any spatiotemporal context into quantal units of where and when events occur, bridging, and thereby organizing events, in a conceptual organization of events (conscious experience). PFC extracts space-time intervals from the hippocampus for the motivational, affective, and cognitive aspects of conscious experience.

Observation and analysis of human conscious experience reveals the organizational structure of human conscious experience. Indications are that human conscious experience has an invariant structural mode of organization based on the three basic types of space-time intervals. This is common to all conscious experiences and to all human beings. This structural mode of organization allows human beings to interpret, understand, and interact with other human beings and allows human beings to interpret, understand, and interact with reality (Sieb, 2018). This characterization of human conscious experience is important for the understanding of consciousness, for the diagnosis and treatment of mental and physical disorders, and for understanding the structural and functional organization of the universe (reality). The three basic types of space-time intervals may be the fundamental elements involved in organization at the microscopic, macroscopic, and cognitive levels. They may eventually be shown to underlie the organizational structure and function of everything (Sieb, 2018).

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