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Theory article

Relating Cortical Wave Dynamics to Learning and Remembering

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Abstract: Electrical waves propagate across sensory and motor cortices in stereotypical patterns. These waves have been described as potentially facilitating sensory processing when they travel through sensory cortex, as guiding movement preparation and performance when they travel across motor cortex, and as possibly promoting synaptic plasticity and the consolidation of memory traces, especially during sleep. Here, an alternative theoretical framework is suggested that integrates Pavlovian hypotheses about learning and cortical function with concepts from contemporary proceduralist theories of memory. The proposed framework postulates that sensory-evoked cortical waves are gradually modified across repeated experiences such that the waves more effectively differentiate sensory events, and so that the waves are more likely to reverberate. It is argued that the qualities of cortical waves—their origins, form, intensity, speed, periodicity, extent, and trajectories—are a function of both the structural organization of neural circuits and ongoing reverberations resulting from previously experienced events. It is hypothesized that experience-dependent cortical plasticity, both in the short- and long-term, modulates the qualities of cortical waves, thereby enabling individuals to make progressively more precise distinctions between complex sensory events, and to reconstruct components of previously experienced events. Unlike most current neurobiological theories of learning and memory mechanisms, this hypothesis does not assume that synaptic plasticity, or any other form of neural plasticity, serves to store physical records of previously experienced events for later reactivation. Rather, the reorganization of cortical circuits may alter the potential for certain wave patterns to arise and persist. Understanding what factors determine the spatiotemporal dynamics of cortical waves, how structural changes affect their qualities, and how wave dynamics relate to both mental experiences and memory-based performances, may provide new insights into the nature of learning and memory.

Keywords: conditioned response; cortical reorganization; forgetting; learning-induced plasticity; retrieval; stimulus generalization; temporal dynamics

1. Introduction

Over a century of scientific studies on the neural substrates of learning and memory have bolstered two dominant views about how memory works. The first, popularized by Franz Gall in the early 1800s, is that distinct brain regions possess specialized capacities for forming, storing, and retrieving memories. The second, promoted by William James and Ramón y Cajal in the late 1800s, proposes that learning leads to physical changes in the connections between neurons that in turn lead to changes in behavior. All current textbooks on the neurobiology of learning and memory present these two ideas as the foundation for current theoretical and experimental studies of memory.

The hypothesis that synaptic plasticity, in particular, is both necessary and sufficient for storing memory traces has spawned thousands of technologically advanced experiments in laboratories around the world (for review, see [1]). Although such studies definitively show that neural transmission can trigger changes in synaptic efficacy that can last for varying lengths of time, and that disruption of these changes can alter learning, some researchers remain skeptical that constellations of synapses constitute memory traces. For example, Gallistel and colleagues [2–4] have argued that a major limitation of the synaptic plasticity hypothesis (SPH) is that it provides no explanation for the known properties of associative learning or memory abilities. Morris and colleagues [1] have countered this critique by suggesting that synaptic plasticity processes can only be directly linked to specific behavioral phenomena associated with learning and memory when one understands the detailed operations of the specific circuits within which synaptic plasticity occurs. A second limitation of the SPH is that it does not directly address the role of other experience-dependent changes in brains that are known to affect neural function, including: synaptogenesis, synaptic pruning, changes in dendritic and axonal structure, neurogenesis, glial plasticity, vascular plasticity, altered metabolic activity, and the redistribution of ion channels throughout a neuron. Although some neuroscientists have argued that such non-synaptic changes are insufficiently specific to provide detailed records of past events [5,6], others have suggested the opposite—that mechanisms such as neurogenesis may enable the formation of more temporally-precise memories than can be achieved by modifying existing synapses [7]. Regardless of one’s views about the adequacy of synaptic plasticity as a mechanism for storing memories or acquiring new associations, it is clear that identifying how synapses change over time, even with high levels of detail and accuracy, is unlikely to provide a complete understanding of the processes underlying learning and memory abilities.

Traditionally, attempts to measure what learning and remembering “look like” in brains have consisted of either intracellular and extracellular electrophysiological recordings from a relatively small number of neurons (mostly in nonhuman animals), or electromagnetic recordings and neuroimages of more distributed activity within brain regions (mainly in humans). These approaches have led to advances in predicting the differential engagement of specific brain regions during learning and recall, as well as detailed descriptions of neural firing patterns associated with task performance. However, exactly what operations the relevant neural circuits are performing when an individual learns something new, remembers a past event, or misremembers an event, remains obscure. Recently, systems neuroscientists have shifted their efforts toward collecting *in vivo* recordings from multielectrode arrays or optical sensors in awake, behaving animals (e.g., [8]). This approach facilitates observations of neural population dynamics that would be difficult to make using earlier approaches, while retaining most of their basic assumptions (including the SPH).

While it is possible that monitoring the activity of hundreds of neurons in parallel will reveal the missing details of neural circuit function that Morris and colleagues [1] claim are necessary to relate synaptic plasticity to learning and memory phenomena, it is also possible that such observations could be used to explore other hypotheses regarding the neural substrates of remembrance. In particular, Pavlov [9] suggested an alternative conceptual framework for understanding how cortical activity contributes to the development of conditioned responses that may be useful in relating the activity of neural ensembles to learning- and memory-related behavioral patterns [10]. He proposed that traveling waves of cortical excitation and inhibition were modified by experience to enable individuals to respond appropriately in familiar situations. In this article, I reconsider Pavlov's cortical wave hypothesis in the light of modern evidence on traveling waves of activity within the brain, as well as recent findings on electrophysiological correlates of discrimination learning. I then attempt to relate this hypothesis to the proposal that memory can be viewed as a form or mode of perception. Finally, I suggest that shifting research emphasis from microanalyses of variations in synaptic efficacy to observational and experimental characterizations of cortical wave dynamics during real-world learning experiences and memory recall performances may provide new insights into the neural substrates of learning and memory.

2. The cortical wave hypothesis

The cortical wave hypothesis (CWH) can be viewed as an extension of earlier theories regarding the reflexive nature of behavior [11,12]. Prior to the work of Pavlov, most researchers interested in reflexes had typically viewed them as "instincts" that were built into an organism's nervous system. Pavlov was impressed by the fact that in different situations, the same stimuli could trigger quite different reflexes (see also [13]). He interpreted this fact as evidence that repeatedly presenting certain stimulus combinations could lead to the formation of supplementary connections in cortex, thereby creating new reflexes (conditioned responses). Some of his key early findings were that the sequencing of stimulus presentations was critical for generating conditioned responses, and that such responses could be acquired even when a conditioned stimulus was no longer present during performance of the conditioned response, suggesting that some internal aftereffects of stimuli were mediating the emergence of conditioned responses. Pavlov performed numerous experiments designed to reveal the conditions that led to the acquisition of conditioned responses. In conducting these experiments, he discovered that different combinations of stimulus pairings could interact within and across training sessions. For instance, a stable conditioned response to a tone could be disrupted if the tone was preceded by a visual stimulus that had been repeatedly experienced without any consequence. Such observations ultimately led Pavlov to conclude that experience-dependent changes in cortical connections could generate both long-lasting increases and decreases in stimulus-induced activity.

Based on his experimental observations, Pavlov proposed that organisms learn to differentiate events by gradually corralling the excitatory, stimulus-induced activity generated in cortical circuits through the effects of inhibitory processes. Importantly, Pavlov [9] did not view the interactions between excitatory and inhibitory processes as a static competition between positive and negative forces (a version of Pavlov's ideas later popularized by Spence [14]). Instead, he postulated dynamic "waves" of activity that varied systematically in strength both spatially and temporally (the CWH); in later descriptions, he suggested that these waves were sometimes periodic. Thus, in contrast to other proposals regarding learning-induced changes in cortical processing such as Hebb's cell assembly hypothesis, Pavlov's hypothesis focused on long- and medium-term variations in the dynamics of cortical activity rather than on the underlying structural changes in circuits. He extended these ideas to try and explain the cortical conditions that occur during hypnosis and sleep and to predict dysfunctional dynamics that could lead to mental disorders. Unlike Hebb's proposals, Pavlov's hypotheses regarding cortical waves and cortical function more generally were widely disparaged soon after appearing in print [15–20]. Common critiques included that behavioral data were insufficient for determining neurophysiological mechanisms and that the kinds of neural activity described by Pavlov were inconsistent with known features of brain structure and function. Consequently, the CWH was quickly discarded, except when it was presented by psychologists as an example of why researchers should not "neurologize" when explaining behavior.

Fundamentally, the CWH assumes the same basic structural mechanisms underlie conditioned responses that Hebb [21] and James [22] proposed were involved in learning, memory, and cognitive skill acquisition. Specifically, Pavlov proposed that repeated coactivation of subpopulations of cortical neurons leads to changes in the strength of the connections between those neurons, thereby increasing the likelihood of their coactivation in later stimulus processing. Like Hebb, Pavlov proposed that the synchronous activation of these subpopulations was transient and occurred in a predictable "phase sequence". Where the CWH diverges from the Hebbian cell assembly hypothesis is that Pavlov hypothesized two kinds of "assemblies": one associated with mutual excitation of neurons and a second associated with inhibition. Furthermore, whereas Hebb postulated that any neurons that were coactive could form an assembly, Pavlov suggested that the topographic arrangement of sensory cortices, as well as their relative "primacy", determined which regions would become more strongly connected during conditioning, as well as the spatiotemporal dynamics of stimulus-induced neural activity before, during, and after conditioning. Finally, Pavlov suggested that interactions between excitatory and inhibitory waves could lead to complex patterns of cortical activity and consequent responding, thereby complicating predictions regarding the strength of conditioned response expression within various training regimens.

3. Properties of cortical waves and related predictions

The CWH was originally developed to account for experience-related variations in the absolute and relative strength of conditioned salivary responses. Despite these humble origins, the hypothesis leads to a number of sophisticated predictions and important research questions. One basic prediction of the CWH is that the postulated waves propagate through the brain from a particular origin and in predictable spatiotemporal patterns. Although each presentation of a stimulus may lead to a slightly different wave pattern depending on past experiences with the stimulus, as well as with other stimuli presented in similar circumstances, the basic qualities of stimulus-evoked wave patterns should recur across multiple presentations and should traverse similar cortical paths. Pavlov [9] suggested that the specific wave patterns that occurred could vary considerably across individuals both in terms of the spatial and temporal scale of activity. Despite these potentially large individual differences, the relative changes in wave patterns associated with training were assumed to be predictable.

According to the CWH, the key variables that determine how stimulus-induced excitatory and inhibitory waves progressively develop are the consistent sequencing of stimulus events and contrasts in the outcomes associated with particular stimuli. Most notably, training that requires an individual to make fine distinctions between similar stimuli should lead to stronger inhibitory effects, which ultimately should increase the individual's ability to behaviorally differentiate those stimuli (e.g., by associating a conditioned response to one stimulus, but not the other).

A third important prediction of the CWH is that the spatial organization of cortical sensitivities should affect the acquisition and generalization of learned responses. If waves of stimulus-induced cortical activity spread throughout cortex, then the effects of such spreading activation should be evident in the response properties of cortical regions other than those directly activated by a presented stimulus. In fact, the generalization of conditioned responses to novel somatosensory stimulation sites was one of the key findings that led Pavlov to originally propose the CWH.

Finally, Pavlov [9] reported that inhibitory after-effects of stimulus presentations could lead to alternating peaks and troughs in conditioned response strength over a period of ten minutes. If propagating inhibitory cortical waves "reverberate" for several minutes, then time-varying effects of such waves should be detectable across multiple trials. These features of cortical waves predict that the timing of trial presentations during training might significantly affect the expression of learned responses as well as the speed of learning.

In the following sections, these predictions and implications are evaluated in light of modern experimental observations of cortical waves as well as correlates of such waves.

3.1. Cortical wave dynamics

Reports of traveling waves of neurophysiological activity have appeared intermittently for decades [23–26], but have garnered little attention from researchers studying the neurobiology of learning and memory. In part, this reflects concerns about the possibility that graded shifts in measures of neurophysiological signals can occur for reasons other than propagating neural activation [25,27], and a general belief that such fluctuations in activity, if relevant at all, most likely serve to facilitate stimulus processing. Evidence from high-density scalp and intracranial recordings has increased confidence that activity does propagate across human cortex in predictable patterns. For example, slow wave oscillations (< 1 Hz) generated during sleep states appear to sweep through the brain at speeds of 1.2–7 m/s [28]; each wave starts at a particular site and propagates at a constant velocity in a relatively steady direction, swelling and then dissipating as it travels. These patterns of wave propagation appear to be consistent across nights and across individuals, with waves more likely to: (1) originate in frontal regions; (2) propagate in anteroposterior directions; and (3) strengthen as sleep deepens. Alpha and theta waves have been observed traveling at similar speeds across cortex in both awake-resting states [29,30] and during stimulus processing [30,31]. Such waves propagate relatively quickly through cortical circuits, but other cortical waves spread much more slowly. For instance, cortical spreading depression, which involves systematic depolarization of expanding regions of cortex, lasts several minutes [32]. At even longer time scales, ultradian rhythms are associated with a periodic waxing and waning of global cortical activity [33]. Although it is not known whether these ultradian rhythms show any sequential patterning in the deactivation and activation of cortical regions, they clearly affect the propagation of activity in ways that are analogous to extremely low frequency (< 2 mHz) cortical waves.

In contrast to the limited observations of propagating cortical waves in humans, there are numerous reports of traveling cortical waves in non-humans (reviewed by [34–36]). Most of the early evidence of traveling cortical waves came from single cell recordings of spike trains, measures of local field potentials, and measures of current source field densities (e.g., [37]). As with early EEG recordings, such measures provided only ambiguous indications of propagation. Development of voltage sensitive dyes (VSDs) changed the situation dramatically. Optical imaging with VSDs made it possible to monitor massively parallel subthreshold intracellular changes in both neurons and glia (e.g., [38–45]), and revealed that propagating cortical waves could be planar or concentric and could travel linearly, curvilinearly, or rotationally [46,47]. In some cases, activity spreads across cortex like a volcanic island rising from the ocean [48,49]. In others, large planar waves may either pass across cortical surfaces or remain stationary (described as standing waves, [50]). Interactions between waves can lead to changes in their direction and velocity [51], as well as their likelihood of generating spiraling waves [52]. The speed, direction, and spatial dispersions of cortical waves depend on the architecture of the circuits within which the waves originated [38,53–57], stimulus features [35], the current brain state [54,57,58], and the sensory context (Figure 1).

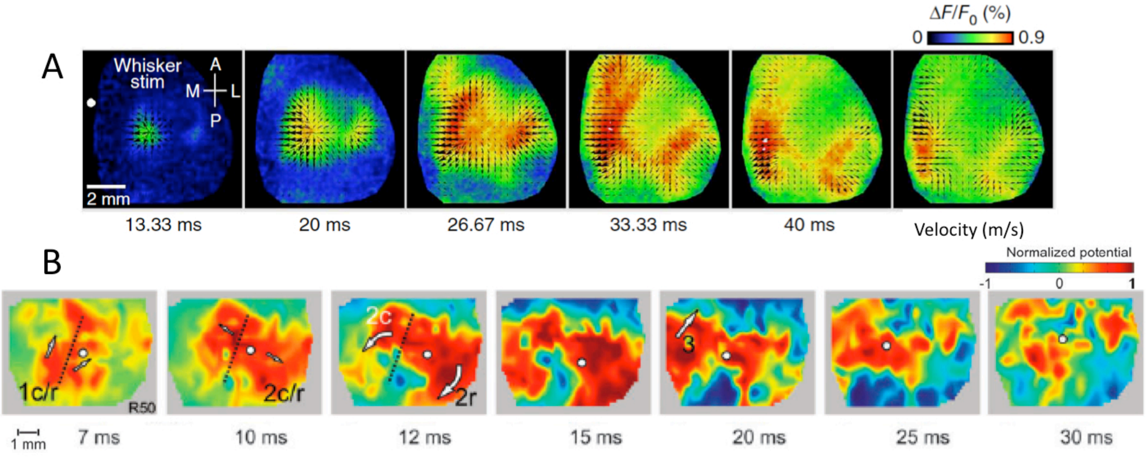

Figure 1. (A) Whisker-stimulation evoked voltage-sensitive dye (VSD) activation at the cortical surface shows cortical waves spreading from a focal point outward. (B) Activation maps of local field potentials evoked by a click show waves in auditory cortex traveling in parallel in adjacent auditory fields; 1=primary; 2=secondary; and 3=tertiary waves. Panels (A) and (B) are modified with permission after [57] and [59] respectively.

As seen in human EEG, spontaneous waves measured with VSDs often originate in numerous locations and propagate in various directions at predictable speeds [51,54,59–62]. Most of the cortical waves studied in animals travel faster than the waves measured with EEG in humans. Waves evoked by stimulus presentations are more predictable in terms of their origins and directions of travel than spontaneous waves [60]. This makes it possible to track their recurrence in the absence of stimulus presentations [57]. Repeated presentations of visual stimuli can lead to increases in the recurrence of evoked waves in the absence of the stimuli for periods of several minutes, with the number of presentations affecting how often and for how long these “reverberations” occur [60]. Waves are often not locked to stimulus onset and may vary in form within [62] and across individuals due to differences in cortical organization or variations in spontaneous activity, making it difficult to track their properties by averaging data across stimulus presentations or individuals [54,60]. Despite such variability, cortical waves do show systematic properties. For instance, in rats, stimulus-evoked traveling waves showed consistent compression when passing across the borders of cortical fields [51].

Neuroscientific studies of cortical waves in non-humans have focused not only on describing their properties, but also on identifying the underlying mechanisms that give rise to these waves. Unsurprisingly, most hypotheses emphasize the architecture of connections to and within cortical networks. Ermentrout [63] suggested three possibilities that could account for the properties of cortical waves: (1) a common source drives activity in cortical neurons at varying delays (giving the false impression of traveling waves); (2) activation spreads via intracortical connections, like a bucket brigade; and (3) weakly coupled oscillatory circuits produce stable phase differences. These proposed mechanisms, which all depend on synaptic transmission, have been incorporated into several past computational models of neural wave propagation [34,64–68]. Other possible mechanisms of neural transmission that could impact wave propagation include ionic diffusion (for slower waves) and electric field transmission [69]. The timing and distribution of neuromodulators within cortical circuits [70], and ongoing cortical activity [44], can also affect the initiation and propagation of cortical waves. Regardless of the specific mechanisms underlying these waves, there is no longer any question that they exist. Cortical waves can be evoked by sensory stimuli, show predictable spatiotemporal dynamics that affect neural responses to similar stimuli, can be modulated by repeated experiences with specific stimuli, and vary across individuals and brain states.

Researchers studying cortical waves have occasionally noted that reverberations associated with these waves share features with Hebb's [21] proposed reverberating cell assemblies, and that such waves might influence experience-related circuit modifications or mediate visual short-term memories and priming [10,60]. Nevertheless, the dominant functional hypotheses associated with cortical waves emphasize their effects on sensory processing. For example, it has been proposed that cortical waves help to encode inputs across distributed networks [10,38], enable scanning of incoming sensory streams [63], provide a mechanism for encoding and transferring information [53], facilitate evoked responses to weak sensory inputs [35], or set the frequency of periodic cortical activity [52]. It is somewhat surprising that less attention has been given to the possible contributions of cortical waves to learning-related cortical reorganization given that waves of excitation in the retina are known to shape connections between the retina and lateral geniculate nucleus [71].

Most of the features of cortical waves postulated by Pavlov [9] have been shown, at least in part, in modern measures of cortical wave propagation. The main differences between his original proposal and current descriptions of cortical waves relate to the variety of wave qualities and their dynamics, differences between spontaneous waves and evoked waves, the prevalence of anisotropic propagation within cortical circuits, the kinds of transformations waves undergo when passing across distinct cortical fields, and the varieties of periodic oscillations within waves. Cortical waves are clearly more complex than Pavlov envisioned. Nevertheless, the key idea underlying the CWH—that waves propagate from predictable origins in predictable spatiotemporal patterns unless they are affected by other wave fronts—has proven to be remarkably accurate given its behavioral origins.

3.2 Excitatory and inhibitory interactions within sensory cortex during discrimination learning

> "*...coordinated inhibition ensures that excitatory activity recruits the right numbers of neurons in the right temporal window and that excitation spreads in the right direction.*"
>
> —Buzsaki [72], p. 65.

Much of what is currently known about interactions between excitatory and inhibitory cortical processes during learning relates to global changes in the relative activation (or suppression) of cortical sensitivities over time. Pavlov [9] postulated that such interactions occurred based on the fact that presentations of a conditioned stimulus paired with no consequence (CS−) suppressed salivary responses to subsequent presentations of stimuli that had been consistently paired with food rewards (CS+). He found that, for somatosensory and auditory stimuli, the degree of suppression varied systematically with the passage of time, and as a function of stimulus similarity (which he inferred was related to the spatial separation of activity evoked in cortical maps). Based on behavioral observations, Pavlov concluded that inhibitory activity evoked by a CS−, as well as excitatory activity evoked by a CS+, initially spread out from the point of cortical activation, and then retreated back toward the origin (Figure 2A), with the specific timing, distribution, and patterning of spreading activity varying across individuals and training regimens. Modern VSD studies provide some support for such patterns of sensory-evoked cortical activity (see Figure 2B), although the time scales that have been analyzed are orders of magnitude shorter than those studied by Pavlov [42].

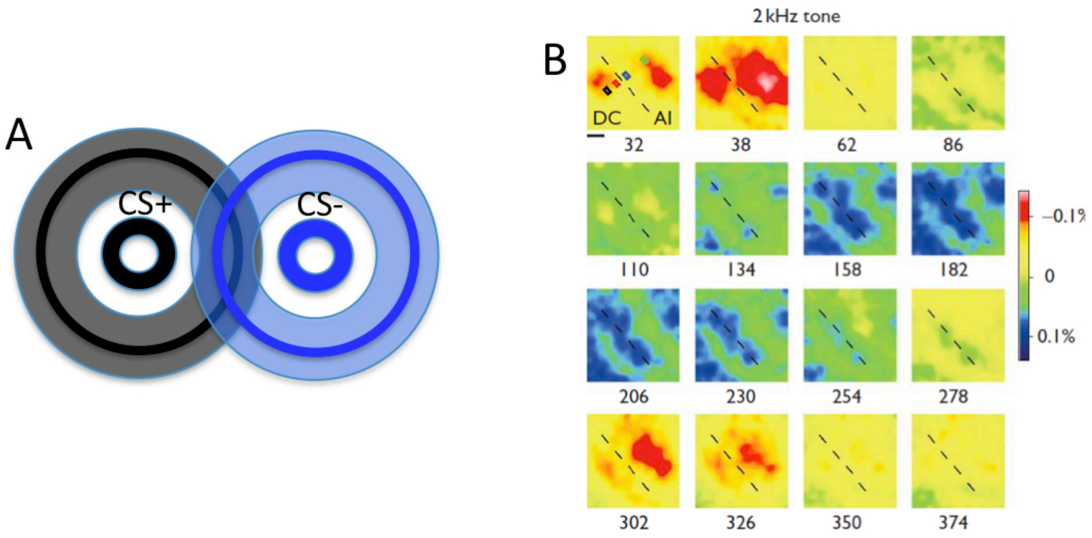

Figure 2. (A) Pavlov hypothesized that stimuli associated with food (CS+) evoke spreading excitatory waves in cortex, whereas stimuli associated with the absence of food (CS−) evoke spreading inhibitory waves. (B) Unconditioned, tone-evoked voltage-sensitive dye activation in auditory cortex shows onset-related excitation spreading outward from two focal points (in two auditory fields), followed by inhibition relative to baseline activity in lateral regions, and later resurgence of excitation. Horizontal scale bar: 1 mm; numbers represent time after stimulus onset in ms. Panel (B) is modified with permission from [42].

VSD measures often do not clearly reveal the effects of excitatory versus inhibitory influences on the formation and movements of cortical waves, because the dyes do not differentiate between intracellular changes within excitatory versus inhibitory neurons [45], and because dye signals are typically processed in ways that obscure global changes in cortical excitability [44]. Recent long-term electrophysiological recordings from monkeys learning to perform auditory and somatosensory discrimination tasks have revealed systematic changes in overall cortical activity that reflect both the type of task the monkey is learning as well as improvements in perceptual acuity over time [73–77]. In particular, operant conditioning tasks involving the discrimination of sounds led to decreases in the excitability of neurons within primary auditory cortex, whereas a classical conditioning task involving the same sounds led to increases [75] (see Figure 3). During six weeks of operant conditioning on a frequency discrimination task, auditory cortical responding was gradually suppressed across the first three weeks of training, when performance was relatively stable [73] (Figure 3A,B). In the fourth week, performance rapidly improved and a relative increase in the excitability of cortical neurons occurred. This global change was followed by further suppression of activity that was more stimulus-specific, with target stimuli being suppressed less than non-targets (similar changes occur during somatosensory discrimination training [74,76,77]). In contrast, classical conditioning with tones was associated with incremental increases in the excitability of sensory cortex [75,78] (Figure 3C). These findings suggest that discrimination learning is associated with broad, incremental changes in the balance between excitatory and inhibitory cortical processes that vary depending on training conditions (see also [79–81]), as originally proposed by Pavlov [9].

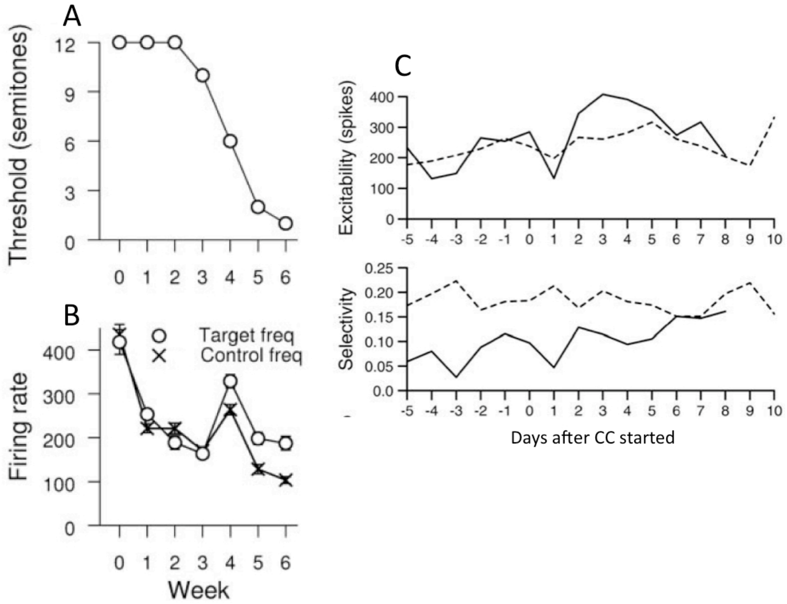

Figure 3. (A) A monkey trained in an operant task to distinguish pure tones shows gradual increases in resolution across six weeks. (B) Measures of tone-evoked responses in auditory cortical neurons initially show a global decrease in responding, then an increase that correlates with large increases in resolution, followed by differential inhibition of non-target tones. (C) Two monkeys (solid and dotted lines) classically conditioned (CC) to distinguish tones both show increases in the responsiveness of auditory cortical neurons to tones, but different changes in the selectivity of responses to target tones, suggesting that different training regimens (operant vs. CC) lead to different changes (decreases vs. increases) in the ratio of excitation to inhibition, and that learning-related changes in inhibition vary across individuals (both monkeys showed conditioned responses). Panels (A/B), and (C) are modified with permission after [73] and [75], respectively.

Traditionally, electrophysiological studies of cortical activity have emphasized stimulus-evoked excitatory responses that reveal the receptive fields of neurons. Measuring stimulus-evoked inhibitory effects is more complicated and depends on the presence of sufficient spontaneous activity [82–85]. Recent work shows, however, that both the excitatory and inhibitory response properties of cortical neurons are modified during training (e.g., [83,84]). For instance, training a ferret to lick for rewards whenever a tone played inhibited auditory cortical responses to that tone, whereas pairing this same tone with a shock led to stronger excitatory responses [83] (see Figure 4).

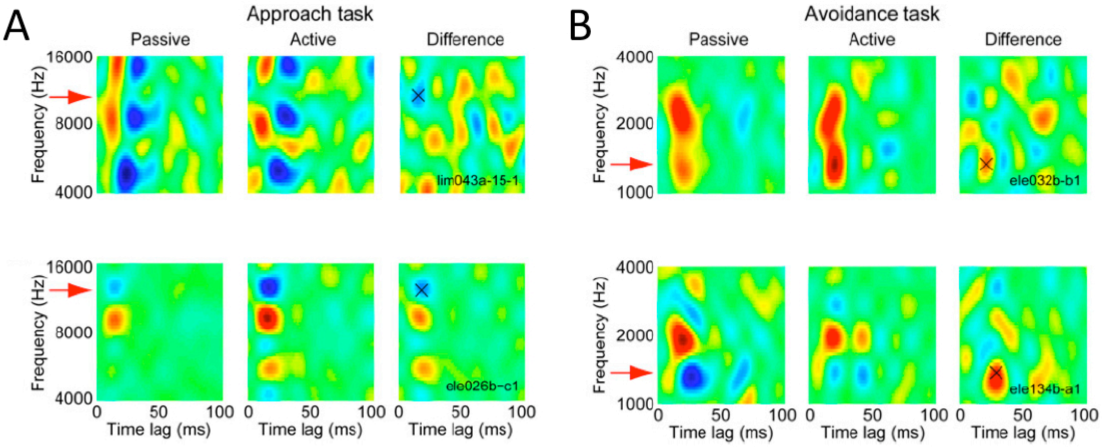

Figure 4. (A) Sample spectrotemporal receptive fields (STRFs) from two auditory cortical neurons (top and bottom) recorded either during passive listening to a tone (indicated by an arrow), or while hearing the tone during performance of a task (“Active”) in which the tone led to licks for rewards, show that neurons responded less to conditioned tones during task performance. Red indicates increased firing (excitation) and blue decreased firing (inhibition). The “×” emphasizes the change in neuronal responses to tone onset between conditions (“Difference”), with blue indicating relatively less onset-evoked neural firing during task performance and red indicating relatively more activity. (B) STRFs recorded from two neurons during passive listening versus listening while performing a task in which particular tones signaled when licks would be punished show that neurons responded more to conditioned tones in this task. Modified with permission after [83].

Although recordings from cortical neurons show that learning experiences change the patterns of cortical activity evoked by sensory stimuli, as Pavlov predicted, it is difficult to extrapolate from measures of receptive fields to the dynamics associated with stimulus-evoked traveling waves. How different learning situations affect the spatiotemporal dynamics of cortical activity thus remains unclear. Nevertheless, current data clearly imply that, to the extent that sensory events evoke cortical waves, the qualities of those waves are likely to change systematically during training as a result of experience-dependent shifts in the balance of excitation and inhibition.

The temporal dynamics of excitatory and inhibitory processes in mammalian cortex appear to be precisely balanced in ways that facilitate the propagation of cortical waves, as well as the rapid modulation of those waves by external stimuli [86]. Additionally, the columnar organization of cortical layers seems to promote propagation of externally triggered network activity [87]. Changes in the properties of stimulus-evoked cortical waves associated with levels of anesthesia support the idea that shifts in the excitatory/inhibitory balance can affect wave propagation, and suggest that high-frequency, localized traveling waves may be particularly sensitive to inhibitory competition [34,54,58]. Models designed to capture the effects of excitatory and inhibitory interactions on the timing and spatial extent of cortical waves may be particularly useful in understanding how cortical waves contribute to learning and memory [34,63].

The functional benefits associated with competitive inhibitory and excitatory processing have been extensively explored within recurrent neural network models of learning, memory, and perception (reviewed by [72,88]). Simulations with connectionist models that incorporate inhibitory competition suggest that variations in the balance of excitatory and inhibitory interactions can strongly determine how learning generalizes to novel situations. However, these simulations often use inhibitory processes primarily to limit the number of neurons that are actively involved in representing learned stimuli (thereby increasing the sparseness of representations). In contrast, electrophysiological studies of discrimination learning in monkeys show that decreases in excitability are associated with an increase in the number of cortical neurons engaged by the stimuli used during training [74]. Additionally, the effects of inhibition on learning-induced cortical changes appear to vary systematically over time, suggesting that cortical plasticity mechanisms may involve processes more analogous to annealing than to a "winner-take-all" competition [89]. These findings are consistent with recent physiological studies showing that inhibitory interneurons can modulate the timing and gain of pyramidal cell firing [90]. Interneurons also can modulate the spatial propagation of neural responses [39,42,91], with the topography of inhibitory effects varying across individuals. For example, models of olfactory discrimination and learning in slugs have shown that inhibitory interactions between the bilateral procerebral lobes (where most odor processing occurs) can control when coherent traveling waves are generated [64]. When inhibition is relatively weak, both lobes produce synchronized traveling waves, whereas when inhibition is strong, one side or the other may be suppressed. Ermentrout and colleagues [64] associate higher levels of inhibition with a learning mode which enables "memory cells" to store information about odors.

Part of the reason why neuroscientists have not differentiated between excitatory and inhibitory cortical waves in the way that Pavlov [9] proposed is that many have incorrectly assumed that stimulus encoding is independent of past consequences associated with earlier presentations of that stimulus (or similar stimuli). Identifying how cortical waves evoked by stimuli with contrasting outcomes differ in form may clarify how the two classes of cortical waves posited by Pavlov (i.e., waves evoked by either appetitive or neutral stimuli) relate to the excitatory and inhibitory processes known to control cortical dynamics and wave propagation. Possibly, learning-dependent changes in the dynamics of excitatory and inhibitory cortical interactions contribute to differences between these two kinds of waves, but further data are needed to evaluate this possibility. The fact that overall cortical state can strongly affect the features of cortical waves implies that both local and global fluctuations in the balance of excitation and inhibition should also modulate wave qualities.

3.3 Topographical constraints on acquisition and generalization

Stimulus generalization is a basic property of learning that is directly related to spatial and temporal properties of cortical activity [92–96]. When an individual learns that a particular stimulus predicts a relevant outcome, leading to a conditioned response, then other similar stimuli may evoke a similar response, even if these stimuli have never previously been experienced [9]. The strength of responding to comparable stimuli depends on both the past training experiences of the individual and on the similarity of cortical activity evoked by the stimuli. Lesioning sensory cortex causes an organism to generalize to a wider range of stimuli [96], whereas discrimination training can greatly increase the specificity of responding (e.g., [73]). Electrophysiological data suggest that behavioral stimulus generalization reflects the degree of overlap of cortical excitation evoked by different stimuli, with response strength reflecting the level of excitation (e.g., [92]). This is true not just for spatial overlap of cortical sensitivities reflecting the topography and intracortical connectivity of sensory cortices [96], but also for temporally overlapping cortical responses. For example, stimuli that evoke similar temporally-structured activity patterns are more likely to evoke similar behavioral responses [92]. The capacity to learn to classify stimuli along particular dimensions also appears to depend on the overlap in cortical responses evoked by variations along those dimensions [97]. Consequently, species with differing cortical topographies show different patterns of generalization after similar training experiences [98].

Stimulus generalization varies as training progresses, with more stimuli evoking conditioned responses earlier in training [9]. Interestingly, the stimuli that lead to the strongest responding after training are often not ones experienced during training, but other novel stimuli that are similar to ones presented during training (e.g., [99,100]). The specific novel stimuli that lead to maximal responding are a function of past training experiences. Furthermore, generalization can depend on the sequencing of trials during training [101]. In some cases, the order of training trials can determine whether it is even possible for an individual to learn fine distinctions between similar stimuli [9,102]. Recent evidence from auditory learning studies in humans further suggests that individual differences in cortical sensitivities within a species may lead to large variations in the acquisition and generalization of learned responses [100]. Given that many features of learning-induced cortical selectivity are reflected in the spatial reorganization of sensory cortical maps [103], it is likely that many of the constraints on sensory learning capacity seen in individuals reflect individual differences in evoked or spontaneous cortical activity patterns [104,105].

Numerous explanations have been proposed to account for stimulus generalization, but few have directly addressed the role of cortical dynamics or cortical topography. Although animals can generalize with no cortex at all [13,96], cortical processing is key for making subtle distinctions between stimuli. Several current models of discrimination and perceptual learning assume that basic associative learning processes account for patterns of stimulus generalization (e.g., [106–108]). Although such models often successfully predict end states of training for group-averaged data, they are less able to predict variations in the temporal dynamics of learning across individuals or species [100,109]. Pavlov [9] noted that individual dogs varied dramatically in terms of both acquisition and generalization, forcing him to postulate that individuals possessed different cortical excitation and inhibition profiles. The SPH, which is basically a neural instantiation of associative learning theories [2], provides no explanation for such idiosyncratic features of either acquisition or generalization, because it assumes that changes to neural connections operate similarly in the neural circuits of all species to produce functionally equivalent stimulus-to-response mappings.

Currently, there are no models of acquisition or generalization that incorporate cortical wave dynamics, and few that attempt to account for spatial variations in cortical sensitivities. Furthermore, the global measures used in most behavioral studies of conditioned responding are not well suited for evaluating the kinds of predictions such models would make (e.g., that the strength of conditioned responding to stimuli will fluctuate systematically over time). Although technical limitations associated with VSDs and long-term implantation of multi-electrode probes have restricted past observations of the spatiotemporal dynamics of cortical activity during behavioral testing, it is possible to track cortical activity from moderately sized populations of cortical neurons while animals are trained and tested with various stimuli (i.e., it is possible to conduct studies of cortical dynamics in individuals during both acquisition and generalization of conditioned responses). For example, multisite optical imaging of piriform cortical activity in anesthetized rats before and after discrimination training revealed that short-latency, stimulus-evoked responses showed greater spreading across cortex after training [110]. Thus, it is not simply technical limitations that have prevented researchers from investigating the spatiotemporal dynamics of cortical activity during acquisition and generalization, but also general assumptions about the types of measures that are most likely to provide information relevant to understanding these dynamic processes (see also [3]).

Perhaps the most extensive work attempting to relate cortical dynamics to learning and memory processes comes from scalp recording studies in humans (e.g., [111]). These studies provide compelling evidence that much of memory-related cortical activity involves oscillations that can be evoked by stimulus presentations and that often originate from predictable cortical locations. Scalp recordings are limited as a means of monitoring cortical waves, however, because they only reveal the cumulative activity of subpopulations of cortical neurons, and provide ambiguous information about the intensity and spatial distribution of activity contributing to these cumulated measures. Despite these limitations, recordings of periodic changes in electrical and magnetic fluctuations of cortical activity make it possible to: (1) monitor learning-related changes in the spatiotemporal activity of large populations of neurons (e.g., [112]); (2) identify individual differences in stimulus-evoked cortical activity that impact learning capacity [113]; and (3) relate differences in training experiences to variations in how cortical activity changes [112]. As noted earlier, scalp recordings provide some of the strongest evidence to date that cortical waves propagate in predictable patterns during sleep in humans, and that such waves can vary systematically across individuals [28]. Correlating detailed measures of individual differences in cortical connectivity (e.g., as measured by diffusion tensor imaging), with either differences in perceptual and memory capacities [114], or with recordings of cortical dynamics during acquisition and generalization, may provide new clues regarding how cortical architecture affects the propagation and function of cortical waves in humans.

3.4 Fluctuations in oscillatory traveling waves modulate learning and memory

Pavlov's [9] finding that the presentation of conditioned inhibitors can sometimes produce spatiotemporally fluctuating effects on the expression of conditioned responses does not appear to have been explored by other investigators, making it difficult to evaluate the replicability or generality of this phenomenon. Recent electrophysiological studies of the hippocampus suggest, however, that the temporal dynamics of traveling waves within this region can affect the acquisition of conditioned responses, and possibly the recall of episodic memories over time. If hippocampal waves intermittently modulate the qualities of propagating cortical waves, then such interactions could potentially account for systematic fluctuations in conditioned stimulus efficacy.

Local field potential oscillations within hippocampal circuits (called theta waves) have been extensively studied, and are thought to play a critical role in coordinating the encoding of stimulus events via memory traces [8,115,116]. For example, Buzsaki [115] proposed that theta waves enhance the formation of spatial maps and episodic memories by chunking stimulus event representations together in time, thereby facilitating the strengthening of connections within associated cell assemblies. Researchers initially had assumed that theta waves occurred synchronously throughout the hippocampus, but recently it was discovered that they actually propagate at predictable speeds along dorsal-to-ventral paths [117,118]. The directionality of theta waves can vary by ± 45 degrees from one wave to the next, and also varies somewhat across individuals. Researchers speculate that traveling theta waves in the hippocampus serve to integrate information in downstream networks [117,118].

Past considerations of the role that theta waves, and other oscillatory brain waves, play in learning, memory, and behavior have focused heavily on correlations between the presence/absence of oscillatory activity and various behavioral states [72,111,115]. There also has been increasing emphasis on correlating oscillatory hippocampal activity with oscillatory activity in other brain regions such as the thalamus [119], cerebellum [120], and prefrontal cortex [121,122], as well as with spiking activity within the hippocampus [8]. Because past studies have focused on what happens when hippocampal theta waves are present rather than on how they spatially propagate or interact with cortical waves, any effects of variations in the directional qualities of traveling theta waves are unknown. What is clear is that the propagation of theta waves within hippocampal circuits is closely associated with learning- and memory-related performances. For instance, researchers found that strong hippocampal theta activity was associated with faster Pavlovian conditioning of eyeblink responses in rabbits [123]. Berry and colleagues [123–125] showed that if trials were triggered on the presence of strong theta activity within the hippocampus, then learning in various classical conditioning tasks was 1.5–4 times faster. Furthermore, eyeblink conditioning that was limited to periods of strong hippocampal theta actually increased the coherence of hippocampal theta waves triggered by conditioned stimuli, which in turn appeared to prolong responses in prefrontal cortex [121]. Also, intracranial recordings from the temporal lobes of patients show large increases in theta activity during the recall of episodic memories [126]. Although these correlational findings do not show that traveling theta waves facilitate conditioning, episodic recall, or coordination of cortical activity related to learning, they strongly suggest that such traveling waves may contribute to learning and memory processes, and that the timing of learning and remembering experiences relative to the spatiotemporal dynamics of such waves is likely to constrain how an individual learns, as well as when they can make use of what they have learned.

4 Relating cortical waves to modern theories of memory

When the cerebral cortex is discussed in relation to memory abilities, it is often described as a storehouse for memories of episodes and facts (e.g., [127]). Pavlovian conditioning, in contrast, is more often associated with memory traces in either the cerebellum (in the case of eyeblink conditioning) or the amygdala (in the case of fear conditioning). These trends reflect a basic assumption of structural views of memory; namely, that memories are physical products of brains within which information is stored long-term. From this perspective, a fundamental question that neuroscientists need to answer is which memories are stored in which places [128]; the mechanism of storage is widely assumed to be synaptic plasticity, regardless of which brain regions are involved. A few psychologists have argued, however, that memory is more usefully thought of as an activity than as a system for storing information (e.g., [129]). A non-intuitive implication of this "proceduralist" view is that, "*the memory trace is perhaps not a specific structure located at some point (or even diffusely) within the central nervous system, but is rather an altered potential of the system to carry out certain mental activities…* [129], p. 200." In this conceptualization, memory abilities are akin to perceptual abilities, and remembering involves distinguishing input-triggered activity patterns—a process dominated by interactions between external events and ongoing mental states. The main questions raised by the proceduralist framework relate more to identifying factors that affect the processing of events and the reenactment of mental operations than to the storage and maintenance of memory traces.

The contrast between structural and proceduralist views of memory is clearest in how they each explain forgetting. Structuralists typically explain forgetting as what happens when stored information becomes degraded over time (e.g., when new experiences lead to changes in synapses that counteract previous changes [127], or when consolidation of synaptic changes is disrupted [1]). Proceduralists instead tend to focus on factors that can lead to retrieval failure, such as interference from other competing mental operations [130]. A key idea in proceduralist explanations of forgetting is that successful retrieval requires that reactivated states be distinctive in some respect from other similar states [131]. For instance, remembered events could be distinctive either with respect to their sensory or semantic qualities (as in the von Restorff effect), or in terms of their temporal features relative to other events [132–136]. If remembering is viewed as discrimination rather than as the retrieval of stored information, then cortical constraints on memory capacity may parallel constraints on perceptual resolution. For example, viewing remembering as a process comparable to perceptual discrimination implies that the success or failure of retrieval should vary as a function of learning in much the same way that stimulus generalization varies with experience. In particular, if training leads to systematic changes in stimulus-evoked wave features that increase the ease with which similar stimuli can be differentiated, then such changes should also increase the ease with which those waves can be regenerated. Successful remembering may similarly depend on progressive modifications to cortical activity patterns and associated increases in the distinctiveness of memory-related states. In this context, the CWH predicts that the likelihood that repeated events would be either remembered or forgotten will reflect experience-dependent changes in the qualities or propagation paths of cortical waves evoked by those events.

The SPH makes no specific claims or predictions about how individuals process either novel or familiar events, or whether this processing has any effect on whether mental operations may be reactivated at a later date. In contrast, the CWH predicts that the spatial topography, diversity of, and interconnections between cortical networks determine both how external events are internally processed, as well as how activity associated with those events can reverberate over time. If voluntary remembering is viewed as an instance of imagining [22], similar to the processes that enable mental rotation of visualized shapes, then it is likely that the same cortical circuits activated by an initial experience will also be engaged during the remembered experience [137]. In other words, the same circuits and mechanisms that enable processing of initial experiences should also enable the reconstitution of past mental operations. The fact that stimulus-evoked cortical waves spontaneously reappear minutes after a visual stimulus was experienced [60], and possibly even hours or days later during sleep [8,138] strongly suggests that neural mechanisms exist for regenerating specific cortical wave patterns associated with past experiences. It remains unclear what enables individuals to differentiate remembered events from ongoing experiences, but presumably these processes would be comparable to those that enable individuals to distinguish internally generated images from externally-evoked images.

The proceduralist view of memory does not attempt to identify specific neural mechanisms underlying different behavioral or perceptual phenomena. Nevertheless, this framework provides a potentially useful way of thinking about how cortical waves may relate not only to the kinds of learning demonstrated in Pavlov's experiments, but also to contemporary studies of human memory. Rather than interpreting learning-related changes in synaptic strengths as constituting the storage of idiosyncratic memory traces, one might instead view such changes, as well as non-synaptic changes to neurons and glia, as adjustments to the "waveguide" of cortical pathways [139] that can potentially change how cortical waves propagate (e.g., their speed and direction), or their form as they propagate. Similarly, tasks that involve active recall of past experiences might be viewed as promoting the reconstruction of previously generated wave patterns, rather than as attempts to retrieve a memory trace stored via a unique constellation of synapses. Under this interpretation, "synapsembles" [8] are not simulacra of previously experienced events that can be selectively reanimated through to-be-determined remembering mechanisms (as proposed by the SPH). Rather, mental experiences (including both percepts and memories) provide the semblance of repetition, despite the fact that the same configuration of synaptic strengths and activations never occurs twice. Synaptic modifications, along with other brain plasticity mechanisms, undoubtedly can shape the qualities, coordination, and extent of cortical activity, including the properties and trajectories of cortical waves. Consequently, much of what has been learned about synaptic plasticity from tests of the SPH is likely to be relevant for understanding experience-related changes in cortical waves.

5 Conclusions

The hypothesis that variations in neural connection strength instantiate memories first gained momentum in the mid-1800s [140]. More recent physiological evidence regarding the specific ways in which synaptic connections change as a function of neural activity are often presented as evidence supportive of this hypothesis [127], and as the foundation for modern neurobiological studies of learning and memory [141]. Although it is often acknowledged that memory traces might also be maintained via the self-sustaining activity of recurrent networks, such processes are generally assumed to be only relevant for transient memories, lasting minutes or less, and largely reflective of longer lasting differences in connection strengths [21]. Recent calls for reconsideration of the primacy of synaptic plasticity as a memory mechanism suggest that: (1) learning involves extracting information from inputs (representational updating); (2) long-term memories are stored via molecular or submolecular mechanisms; and (3) long-term memories are retrieved via some to-be-determined read/write mechanism [2–4]. This alternative hypothesis shifts the location, substrate, and content of the memory trace, but retains the basic assumption, originally proposed by the early "mental physiologists," that remembering involves reactivating dormant engrams to thereby replay previously experienced events.

Pavlov's [9] proposed neural mechanism of learning (the CWH) is compatible with the idea that synaptic plasticity is an important underlying mechanism of memory. In fact, he specifically proposed that progressive changes in the spatiotemporal dynamics of learning-induced cortical waves were a consequence of adaptive strengthening of neural connections. Unlike modern theorists, however, Pavlov did not assume that stronger connections constituted memories stored for later replay. Instead, he suggested that plasticity within cortex led to systematic modifications in the qualities of stimulus-evoked propagating waves that increased or decreased their excitatory and inhibitory effects, an idea largely driven by his experimental results. Under this interpretation, the disposition of the brain to respond in particular ways changes as a function of conditioning, but the specific connections that change (and the relative permanence of such changes) are less critical for supporting conditioned responses than are the particular cortical wave patterns evoked by ongoing events. Thus, there need not be fixed, localizable changes in specific synapses in order for the brain to regenerate cortical waves similar to those evoked by past experiences. As in proceduralist theories of memory, all that is required is that the likelihood of particular mental states occurring is altered.

To a certain extent, the basic assumptions of the CWH seem contrary to the idea that cortical neurons represent events through selective tuning to specific features [35,57]. Why create "matched filters" in cortex for particular sensory features if activity generated by such feature-detecting neurons will potentially spread to millions of other neurons that are not specifically tuned to those features? In contrast, the specificity of memory traces assumed by the SPH, and related structural theories of memory, seems more consistent with the idea that cortical networks serve primarily to efficiently encode idiosyncratic activity patterns. Cortical waves, which are intrinsically dynamic and fleeting, may seem less well suited for mediating learning or memory processes. It is important to keep in mind, however, that the origin, strength, and form of cortical waves is a function of the cortical sensitivities of individual neurons, such that the encoding specificity of cortical neurons contributes directly to the spatiotemporal dynamics of cortical waves. Consequently, cortical waves retain the representational benefits associated with decomposition of stimuli into "primitives," while affording opportunities for complex interactions between cortical activity patterns that might be difficult to replicate via processing by individual neurons. Understanding how cortical waves interact may be particularly important for assessing their contributions to conditioning and remembering.

In thinking about how cortical waves might relate to learning and memory, it is useful to consider how similar waves of neural activity enable animals to move. In insects and lampreys, for example, locomotion is an emergent feature of traveling oscillatory waves of neural activity, not a piece of information or a program that is retrieved from stored "movement traces" within an animal's nervous system. Remembering might similarly be thought of as an emergent feature of cortical wave propagation. As in locomotion, traveling cortical waves may be particularly advantageous in situations involving repetitious, temporally precise circuit activation, as well as for integrating the activities of multiple circuit components. Researchers studying the propagation of neural activity within the hippocampus (a brain region widely believed to play a key role in learning and memory processes) similarly have noted that traveling oscillatory waves may facilitate the integration of information from multiple cortical regions [117,118].

The relationship between traveling waves and more static oscillatory patterns of activity remains unclear. Ermentrout and Kleinfeld [63] suggested that traveling oscillatory waves occurred in the absence of external stimulation, whereas stationary, synchronized oscillations were associated with external triggers. In contrast, Benucci and colleagues found that variations in the position of a visual stimulus produced traveling waves, whereas variations along a second dimension (orientation) produced standing waves [50], leading them to suggest that different cortical connectivity patterns associated with feature selectivity may be more or less conducive to wave propagation. Buzsaki [72] proposed that the resonance properties of individual neurons naturally lead to oscillatory waves and that synchronous oscillations are an energetically efficient way to enhance the effect of a population of firing neurons, implying that static oscillatory states might be a default mode of self-organized population activity. Recent research showing that complex cortical wave patterns may, in some cases, be synchronized across hemispheres [46] suggests that the temporal dynamics of cortical wave propagation may be more precisely coordinated across broad cortical networks than has generally been assumed (i.e., the spatiotemporal dynamics of propagating waves in different cortical regions may be synchronized just as oscillatory patterns in separate regions are sometimes synchronized). Ultimately, whether variations in the propagation of oscillatory patterns of cortical activity (or lack thereof) affect learning and memory abilities is an empirical question that can best be addressed by actually observing and manipulating such patterns as individuals learn and remember.

Cross-species comparisons can provide new insights into how variations in cortical architecture affect the qualities of cortical waves, and the extent to which such variations constrain learning and memory capacity [104]. Similarly, developmental studies can reveal whether the features of cortical waves vary systematically with age, as suggested by the gradual refinement of sensory cortical map organization during development. Although studies in behaving animals hold the greatest promise for testing the CWH, it remains possible that human studies might be particularly critical for relating certain types of memory experiences to the dynamics of cortical waves. For instance, subjective memory-related phenomena such as *déjà vu*, which are associated with aberrant traveling waves within perirhinal and entorhinal cortices in patients with epilepsy [142–144], may provide important clues regarding how cortical waves relate to the feelings that distinguish remembered experiences from the perception of ongoing events. Proponents of the SPH have seldom addressed how one might subjectively distinguish "replay" of a previous neural state from the original experience. The ability to observe or stimulate the illusion of repetition may be critical to clarifying this key aspect of remembering, as well as for understanding how the properties of cortical waves might reflect or drive such subjective impressions.

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Conflict of Interest

The author declares no conflicts of interest in this paper.

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