Temporal Memory Traces as Anticipatory Mechanisms

Peter Cariani

Abstract Brains can be considered as goal-seeking correlation systems that use past experience to predict future events so as to guide appropriate behavior. Brains can also be considered as neural signal processing systems that utilize temporal codes, neural timing architectures operating on them, and time-domain, tape-recorder-like memory mechanisms that store and recall temporal spike patterns. If temporal memory traces can also be read out in faster-than-real-time, then these can serve as an advisory mechanism to guide prospective behavior by simulating the neural signals generated from time courses of past events, actions, and the respective hedonic consequences that previously occurred under similar circumstances. Short-term memory stores based on active regeneration of neuronal signals in networks of delay paths could subserve short-term temporal expectancies based on recent history. Polymer-based molecular mechanisms that map time-to-polymer chain position and vice versa could provide vehicles for storing and reading out permanent, long-term memory traces.

Keywords Neural timing nets · Neural codes · Pitch · Rhythm · Auditory scene analysis · Temporal codes · Expectancy · Music perception · Engram

1 Introduction

As the aphorism goes, "the purpose of remembering the past is to predict the future." Anticipation involves both predicting future situations and events and preparing for them. Anticipation not only projects *what* will occur but also *when* and *where* it will occur, as well as what to do about it. Anticipatory mechanisms enable organisms to use past experience to act in a manner appropriate for future conditions. This chapter proposes novel anticipatory neural memory mechanisms that are based on neural time codes and temporal pattern memory traces.

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2 Anticipatory Systems

"Anticipation" is a general notion. The theoretical biologist Robert Rosen coined the specific term "anticipatory system" [1–3] and defined it as a system in which prospective future states determine present behaviors [4]. The papers in this volume are the product of the last of three conferences inspired by Rosen's and Nadin's ideas about anticipatory systems [5, 6].

2.1 *Purposive Systems as Functional Organizations*

Anticipatory systems are those systems that have embedded goal-states: they are organized in such a way that their action realizes desired future states. The idea has much in common with naturalistically grounded teleologies ("teleonomies") of purposive systems. In the east, Russian physiologists and psychologists (Anokhin, Sudakov, Bernstein, et al.) developed general theories of functional systems [7–9]. In the west, notions of purposive, feedback control systems formed the basis of the early cybernetics movement [10–14].

Rosen and his mentor, Nicolas Rashevsky, were strong proponents of a non-reductionist, relational, theoretical biology that focused on questions of *organization* as explanations of functions, rather than appeal to mechanistic reductionism [15, 16]. Rosen offered the parable of an amoeba in a pot of water, before and after boiling. The live amoeba and the dead one share the same molecular constituents, but the organization of the system has been altered by boiling in such a way that the amoeba was no longer able to regenerate its parts and its organization. Rosen mounted deep criticisms of the machine and computer metaphors for describing living systems, not because the parts in some way violate the laws of physics, but because, in describing living systems solely in terms of trajectories of parts, one misses the organizational relations that make the system a persistent, coherent entity. Knowledge of parts is useful certainly for designing drugs, but it does alone not tell us how to go about building stable, regenerative organisms [17]. For that, as Rashevsky and Rosen foresaw, one needs a theory of mutually stabilizing relations.[1]

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[1] Such biological system theories have deep implications for medicine. Much of our current understanding of disease in terms of "molecular medicine" is grounded in linear chains of interactions between molecular parts. Many therapies simplistically attempt to control one variable (e.g., blood sugar concentrations) using one or two interventions (insulin) without considering the circular-causal nature of networks of metabolic loops that can stymie such interventions. Only if we are able to model the whole set of systemic interactions and relations can we anticipate what the system will do in the short and long term. Once we have an adequate systems theory of biological organization, we will gain the deeper understanding needed for how to design therapeutic interventions that have self-sustaining effects such that the need for further interventions becomes self-limiting.

2.2 Anticipatory Systems in Animals with Nervous Systems

Although the most obvious examples of anticipation involve animal behaviors mediated by learning and memory, many non-neural examples of biological anticipatory capabilities abound. For example, in many plants and animals, developmental stages are orchestrated to occur at favorable seasons of the year (e.g., seed germination in early spring). The mechanisms for favorable timing of developmental stages arise in environments with strong seasonal variations. The environmental variations create positive selective pressures for anticipation, such that those lineages, whose individual time development enhances survival and reproduction, will tend to persist longer than those that don't. Because of the cyclical, predictable nature of seasonal changes, timing strategies that worked better in previous cycles will continue to work better in present and future cycles. Thus anticipatory timing mechanisms appropriate for coping with the future can evolve, provided that similar situations recur.

Animals are motile organisms that cannot produce their own food. In contrast to fungi, which absorb nutrients, animals ingest and digest their food. As a consequence, most animals must move to find food, such that the immediate environments within which they must orient and transport themselves are ever changing. Animal lineages evolved nervous systems that coordinate the actions of effector organs contingent on the sensed states of immediate surrounds and on current internal goal-related states. Embedded goal-related states include the needs of the organism for survival (e.g., satisfaction of system-goals of homeostasis, self-repair, growth), and reproduction. Those lineages of organisms that evolved more effective embedded goal mechanisms for survival and reproduction tended to persist. In choosing actions contingent on percepts and active goals, organisms in effect anticipate which actions will be most appropriate in satisfying those goals.

On evolutionary timescales, variation, construction, and selection processes yield organisms that are better adapted in their particular ecological contexts for more reliable (survival and) reproduction. During the lifespans of organisms with nervous systems, neural learning processes shape percept-action mappings contingent on past experience and reward. So even in the most primitive kind of adaptive percept-action systems, there is anticipation in the sense that the results of previous experiences and successful performances continually modify system structure and behavior to guide future action.

In both evolution and learning cases, memory mechanisms encode the past and make it available for anticipation of what actions can be most appropriate in the current state. In the evolutionary case, the memory lies (mostly) in the genetic sequences that, shaped by selective pressures and construction constraints, persisted in the lineage. In the learning case, the memory lies in short-term memory traces that guide behavior based on the immediate past and present, and in more permanent long-term memory traces that can guide behavior that is based on the deeper past.

2.3 Organization of Perception and Action

Animals with nervous systems can be characterized in terms of purposive, percept-action systems. They have sensory receptors that permit them to make distinctions on their surrounds; effector organs (mainly muscles) that permit them to influence their environs (action); and nervous systems that permit coordination of action contingent on behavior. Aside from sleep or other dormant states, there is a constant, ongoing cycle of percepts, coordinations, actions, and subsequent environmental changes (Fig. 1, bold arrows).

In parallel with percept-action cycles are internal cyclical neuronal dynamics that steer behavior from moment to moment and over the long run (Fig. 2). These include the neuronal dynamics of competing internal goals, internal modal system-states (e.g., waking/sleeping, affective states), cognitive and deliberative processes, attention, action-selection, and the influence of long-term memories.

Embedded in all nervous systems of animals are feedback-driven goal mechanisms that steer behavior in a manner that reliably satisfy basic organismic imperatives of survival and reproduction (e.g., maintain oxygen/water homeostasis, find food sources, avoid predators, find mates). Competitive dynamics of current goals determine which goals are paramount at any given moment such that their

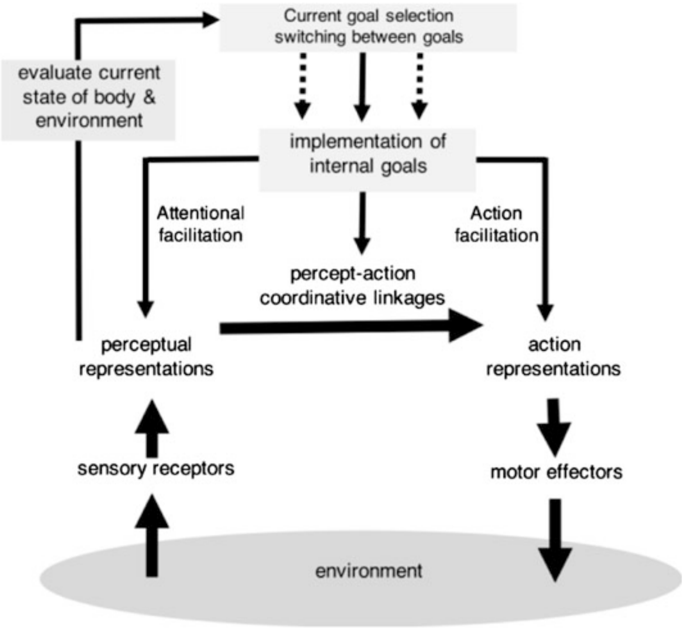

Fig. 1 Percept-coordination-action cycles and goal-directed steering of percept-action coordinations

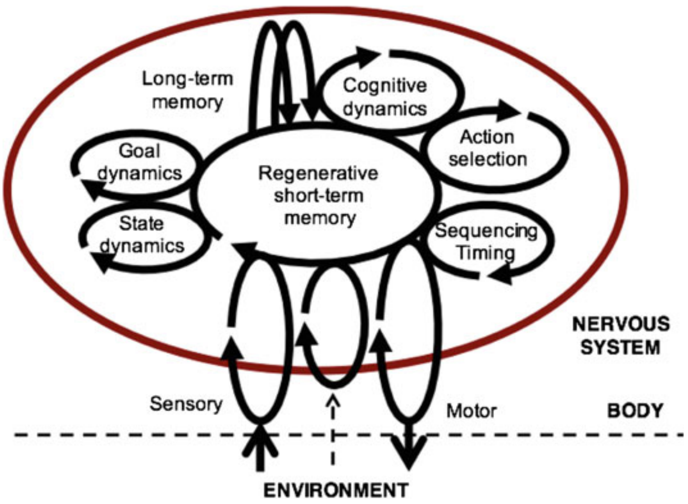

Fig. 2 Functional organization of informational dynamics in brains

drive states partially determine behavioral choices (action selections).[2] This is basically "dominance principle" of the Russian psychologist Ukhtomsky (1845–1942) [9]:

> … in the nervous system, there is at each moment only one active dominating dynamic structure or constellation of excitation, which is associated with the most actual, urgent ongoing needs and desires. This excitation structure plays the role of a situational nervous network, an agency for organizing the physiological and behavioral response directed to satisfying these needs. At the same time all other goals and desires are suppressed" [18]. What is the difference between a bodily physiological mechanism in an animal and a technical mechanism? Firstly, the former is generated during the course of the reaction itself. Secondly, once chosen, the behavior of a technical mechanism is secured once and for all by its construction, whereas in a reflex apparatus it's possible to successively realize as many different mechanisms as there are available degrees of freedom in the system. Each of the successively realized mechanisms is achieved through the active inhibition of all available processes, except one. (Ukhtomsky, quoted in [18])

The notion of competitive goal dynamics fits extremely well into current conceptions of brains as sets of competing circuits that steer behavior, for better or worse, towards particular sets of goals ("implementation of internal goals" in Fig. 1). The notion of the inhibitory suppression of non-dominant goals fits very well with the emerging conception of the basal ganglia/striatum as a generalized double-inhibition braking system in which brakes are selectively released to

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[2] Drive states only partially determine actions, because arguably, actions taken also depend upon which action-alternatives (affordances) are perceived by the organism to be immediately available. Those goals that have obvious, apparent means of attainment may be more attractive for action. Perception of options for effective action can feed back to change which drive states become dominant.

facilitate task-relevant thalamic sensory and motor channels. The resting state is a state of inhibition of sensory and motor systems in which neural loop gains are slightly attenuating. The release of inhibition changes these gains to slightly amplifying, thereby facilitating neuronal sensory and motor signals related to the current dominant goal.

In addition to competitive goal dynamics, virtually all animals switch their global system-states between discrete modes of operation and behavior, (e.g., waking-sleep-hibernation cycles and behavioral modes such as eating, excreting, hunting, fleeing, communicating, exploring, mating) [19]. Affective states, which can be regarded as internal assessments of the current overall "state of the organism" also modulate behavior choices by increasing propensities for different modes of action (e.g., fight/flee/approach). Behavior is jointly determined by internal states (goal-drive state, system-mode, affective states), as well as by the perceived current state of the environment and the perceived goal-satisfaction action-possibilities that the situation affords (Fig. 1). The situation perceived by the animal is in turn jointly determined by the state of the environment and the animal's perceptual systems.

2.4 General Types of Functional Organizations

In my view, such animals can be categorized in terms of the functionalities that their organizations afford. Animals are *living systems* because they actively regenerate their organization (material components and relations). This is the core idea underlying conceptions of self-production systems [20], autopoietic systems [21, 22], metabolism-repair systems [23, 24], self-reproducing robots [25], autocatalytic nets [26], self-modifying systems [27], and semantically-closed self-interpreting construction systems [28]. They are *semiotic systems* because their internal operation and resulting behavior can be described in terms of sign distinctions conveyed via neural codes [29, 30]; and they are *autonomous purposive systems* because they are mainly driven by internal goals.

They have their own *agency* to the extent that they have embedded goals (internal motivation), requisite ability (the right mechanisms needed for action), and sufficient freedom of action (autonomy) to reliably achieve particular goals. They are *anticipatory systems* if they have learning and memory mechanisms that allow them to project the past into the present so as to evaluate future consequences of current courses of action. If one defines these different attributes in terms of these specific kinds of material organizations, then a system, such as an autonomous robot, need not be living to be semiotic, autonomous, purposive, or anticipatory, or to exhibit agency. Underlying these different types of functional organization is the Aristotelian notion of *hylomorphism*.

2.5 *Hylomorphism as an Ontology for Functional Organization*

Hylomorphism is an ontology of functional organizations embedded in matter. Aristotle adopted the hylomorphic framework in formulating his theories of life and mind [31–33].

Life, purpose, meaning, and even conscious awareness are properties of material systems that are organized in particular ways. Explanations based on organization (the system is organized so as to realize a particular goal, i.e., it has a "final cause") are complementary to reductionist, causal explanations based solely on physical properties of parts. Purposive, goal-directed systems are material systems that are organized so as to realize particular goal end-states that in effect become their final causes.

An example of a simple purposive system is a thermostatically regulated heating system that is organized so as to maintain the temperature of a room within a particular range. The "final cause" of the system is the end-state target temperature range that is determined by the thermostat. (Because of its organization and material realization, the system seeks the corresponding temperature states, and, provided that the system is working properly, the thermostat setting "predicts" the final temperature state of the system.)

Hylomorphism is a functionalist ontology to the extent that functional organization can be abstracted from particular material substrates. One can design a thermostatically regulated heating system in terms of functions of and relations between components without specifying exactly how thermostat control mechanisms and heating/cooling elements are to be realized materially (and different material implementations can realize comparable behavioral functions). However, unlike platonic ontologies based entirely on ideal forms, a hylomorphic ontology is materially grounded. In order to realize functions within the material world, organizations must be realized in *some* material form. It is not enough to replicate form; the organization must be fleshed out, embodied, such that it interacts with and changes other parts of the material world.

3 Anticipation and Memory

Memory is a process that entails the maintenance of a distinction through time, and thus it is a semiotic process that is invariant with respect to time. Anticipatory prediction involves estimating the course of future events based on the (remembered) past and present (Fig. 3).

Nervous systems evolved to coordinate behavior. Coordination without memory is possible where mappings between percepts and actions do not change with experience. However, once these coordinative mappings can be modified on the basis of experience, then the effects of past experiences can carry over into present

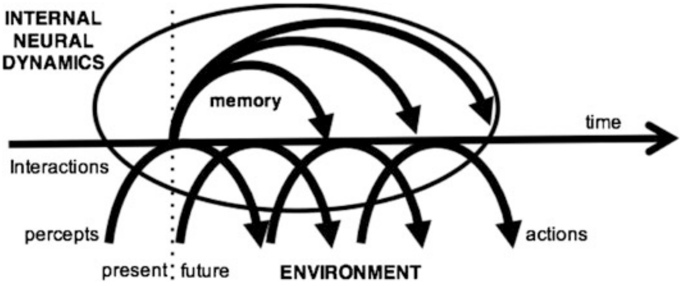

Fig. 3 Memory enables present distinctions to carry over to influence future actions

and future. This kind of simple adaptive modification of behavior does not require explicit storage and retrieval processes.

In biological organisms and nervous systems, anticipation involves not only *what* situations and events are expected, but also *when* and *where* they are expected to occur. In animals with nervous systems, anticipation involves (usually implicit) understanding of the contingent structure of the world (modeling) for deliberative purposes: to decide whether positive action needs to be taken, to determine what actions are available (perceived affordances), and if so, what action is most likely to satisfy those system-goals that are currently of highest priority (goal satisfaction).

3.1 Short- and Long-Term Memory

Standard theories of memory posit a labile, short-term memory coupled with a permanent long-term memory (Fig. 4). There is large literature, old and new, in psychology on the characteristics and nature of memory [34–36]. Many treatments further subdivide different types of memory by modality, the nature of the items stored, temporal processing windows, and temporal persistence, while others seek universal frameworks.

Short-term memory, broadly construed, provides a temporary store of neural signals related to current and recent perceptions, thoughts, affects, motivations, as well items maintained via working memory or recalled from long-term memory. Since the 1930s, the neural mechanisms that subserve short-term memory have been conceived explicitly in terms of neuronal reverberatory processes, i.e., neural activity patterns that are actively maintained and self-sustaining. The sustained firing of neurons that permits these activity patterns to persist is facilitated by activation of N-methyl-D-aspartate (NMDA) receptors that create the biophysical conditions for long-term potentiation (LTP) and spike-timing-dependent plasticity (STDP).

How the specific contents of these temporary memories are coded in neuronal activity patterns is the neural coding problem as it applies to memory. If the

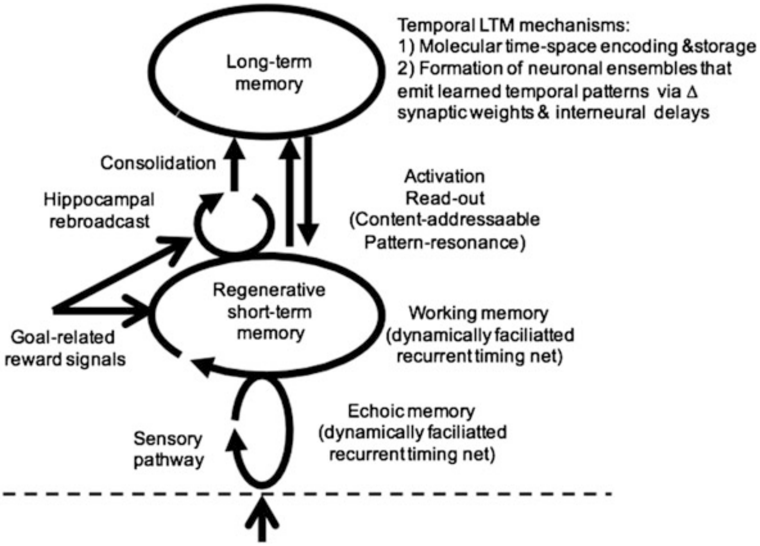

Fig. 4 Short-term regenerative memory and long-term memory. Neuronal signals related to current goal-states are maintained in regenerative short-term working memory and eventually consolidated into long-term memory traces. In this proposed scheme, the contents of short-term memory stores consist of complex temporal spike patterns that are actively regenerated in correlation-facilitated delay paths. Long-term temporal memory traces are activated by corresponding temporal patterns present in working memory, enabling pattern-resonance and content-addressability

information is encoded such that specific subsets of neurons have sustained, elevated firing rates, then the reverberating patterns likely involve persistent activation of these specific neuron subsets. If information is encoded in temporal spike patterns, as is proposed here, then the reverberating patterns likely involve persistent regeneration of spike patterns within neuronal circuits.

The hippocampal formation is the bridge between short-term and long-term memory stores. It appears to be responsible both for maintaining neural activity patterns in short-term memory and for replaying neuronal patterns associated with significant events such that they can be consolidated into long-term memory, mainly during sleep. This work originally came out of animal maze-running experiments, where "place cells," which encode distinct maze locations, were observed to fire in the temporal sequences of the maze running. Recently, "time cells," which encode the timings of events and places, have been found in the hippocampus and elsewhere [37]. During states of sleep or during periods of awake reflection, stored event-sequences can be replayed at faster-than-real-time, enabling them to function as predictive reward mechanisms [38].

Long-term memory is permanent: it can survive sleep, seizure, general anesthesia, and long periods of coma. Once formed, some types of long-term memories can last the entire lifetime of an individual.

3.2 Music, Memory, and Anticipation

Music perception offers a rich set of examples of the actions of short- and long-term memory mechanisms whose operations span timescales from seconds to lifetimes [39, 40]. Because music is a universally familiar medium that involves sequences of discrete events that unfold in time within the evolving context of the remembered recent present, it provides an excellent springboard for studying the role of time in mind and brain.

In music, every note-event creates an expectancy of the next note-event such that sequences of notes create pattern expectancies of succeeding notes. Repeating a sequence of events immediately groups the events in the sequence into a coherent "chunk" and creates a strong expectancy that the pattern sequence will repeat yet again. The pattern expectancies can involve temporal patterns of the note timings (rhythmic patterns), note accent patterns (meter), pitch sequences (motifs, melodies), and timbral sequences. Temporal grouping processes, which were extensively investigated by the Gestaltists, play an essential role in shaping these expectancies [39, 41, 42].

The brain is extremely good at detecting patterns of events and attributes that recur, and it can do this over many timescales.[3] In music, periodic sound patterns whose waveforms rapidly repeat (25–4000 Hz) produce musical pitches (that can carry a melody), whereas slower periodic patterns of sonic events (10 Hz or less), be they musical notes, clangs, or speech fragments, create rhythmic expectancies. Every repeating sound creates a strong expectancy of its continuation, and violations of this expectancy are highly noticeable. The repeating pattern is grouped into a unitary whole (a "chunk"). If the pattern is a fast-repeating acoustic waveform with a repetition rate greater than about 25 Hz, we perceive a pitch at the repetition rate. The tonal quality (timbre) of the sustained sound is determined by the form of the repeated waveform (or in Fourier terms, its spectral distribution and shape).

In music, repeating temporal patterns of onsets and offsets of discrete events with rates of less than roughly 10 per second are perceived as rhythms. Different temporal patterns are heard as different rhythms. Here the repeating events are grouped together into a chunk ("groove"), and after a few repetitions, expectations that each of the events will recur at a given time in the sequence and with the same attributes rapidly develop. This implies that the representation of the rhythmic pattern contains not only information about the sequence of events and their respective attributes (e.g., pitch, timbre, loudness, duration, location), but also a timeline of events. The memory trace of a rhythmic pattern essentially replicates the timeline of the events (the timings of event onsets, mainly, but also offsets that co-encode event-durations).

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[3] Oliver Selfridge once related to me his experience with early computers with mechanical relays. The programmers would set up the computer and would stay in the room periods of time while the computations ran. After a while they would begin to notice long and elaborate repeating irregular sound patterns that were being produced by the relays as the program executed long, iterated complex instruction loops.

What is the nature of this memory trace? Although it has been conventionally assumed that temporal relations are converted to spatial patterns of neuronal activation, there have been a number of suggestions in the past that the memory traces themselves might be temporal patterns. In his book on the psychology of time, Fraisse [43] references the "cyclochronism" theory of the Russian psychologist Popov. Longuet-Higgins had proposed various nonlocal, holographic memory schemes based on frequency-domain Fourier decompositions (holophone model, [44]). Although these have the merit of using the oscillatory dynamics of neural populations, they had very limited storage capacity. Much more promising was a later time-domain mechanism based on temporal correlations between spikes [45]. Roy John proposed that evoked, induced, and triggered temporal patterns of response could subserve general mechanisms for memory [34, 46, 47].

We propose that temporal patterns of spikes might provide a direct basis for temporal memory trace mechanisms. In essence, temporally patterned stimuli impress their temporal structure on the time structure of neural spikes, such that the temporal patterns of spikes can serve as an iconic time-domain representation of the stimulus.

A great deal of evidence in the auditory system points towards temporal codes for pitch and rhythm, albeit at different levels of the system. The most obvious neural correlates of musical pitch lie in spike timing patterns— distributions of interspike intervals—in the auditory nerve, brainstem, and midbrain [48, 49]. Those for rhythm can be found at all levels of the system, from auditory nerve to auditory cortex and beyond. The onsets and offsets of every note produce well-timed spikes in large numbers of cortical neurons [50], such that temporal patterns of note-events replicate the temporal structures of their rhythms [51, 52]. These evoked neuronal temporal responses provide the necessary inputs for various oscillatory mechanisms of rhythmic and metrical expectancy that have been proposed [53]. (Possible direct time codes for rhythm and their relationship to oscillatory dynamics are discussed a bit more below in Sect. 5.2.2.)

3.3 Mismatch Negativity and Short-Term Expectancies

Short-term musical memory is very sensitive to the timing of events; and there are neural responses that are widely observed in event potentials that appear to be related to short-term temporal expectancies and their violations. Event potentials are averaged electrical or magnetic signals triggered (aligned in time) by the onset of a particular event, such as a note-event or even the change in a note-event pattern.

A so-called "mismatch negativity response" (MMN) is observed when an event is presented repetitively ("standard") and then some change is made in a subsequent event ("deviant"). Such MMN-like responses are widely used to study the dynamics of musical expectancies and their violations [50, 54, 55].

If the event is a musical note, any perceptible change in the physical attributes of the note, such as a change in sound level (loudness), periodicity (pitch), spectrum (timbre), attack (timbre), duration, or location (apparent location), will produce a neural response that differs from the response to the standard event. Here the context of the standard event pattern has created an expectancy that is then violated by the deviant event. The mismatch negativity is computed by subtracting the time-pattern of the averaged response to deviant events (triggered on their onsets) from that of the standards. Depending on the nature of the change in events, the mismatch negativity peaks at a characteristic latency after the beginning of the deviation from the standard, i.e., at the onset of the deviant stimulus. This latency is typically on the order of 100-200 ms for changes in basic auditory perceptual attributes.

The MMN is evoked more or less automatically. It does not require subjects to attend to the stimuli, and indeed can be observed in sleeping subjects, infants, and many animals. MMN responses to a standard metrical musical pattern followed by the same (syncopated) pattern in which one of the beats is omitted are observed in newborn infants. MMN-like responses are observed (sometimes reported under a different name) in many different species, sensory modalities, and brain regions.

MMN-like responses can also be seen for “higher level” patterns and attributes. Complex rhythmic and/or melodic patterns of note-events can be presented as standards, and a pattern that deviates in some respect (e.g., a change in the periodicity (pitch) of one of the notes) will create an MMN closely following the time point of the deviation. MMN-like responses with longer latencies are observed for syntactic and semantic violations and yet other kinds of more abstract attributes.

MMN responses are sensitive not only to changes in the perceptual and cognitive attributes of discrete events, but also to their timings. If a regular metrical sequence is set up as the expected standard pattern, then deviations in the timing of subsequent events (leads or lags relative to the expected timing of the beat) will evoke MMN responses, again with a latency that depends on the timing of the expectancy-violating mismatch. In music, these expectancy violations form the basis for expressive timing, intentional manipulation of the timings of notes to convey and evoke emotions.

MMN phenomena suggest the existence of canonical neural temporal comparison mechanisms. It is as if a timeline of events is being built up, maintained in short-term memory, and compared with incoming temporal patterns. In this chapter, I propose a complex neural time code in which both the attributes of events and their relative timings are encoded and simple neuronal delay-and-compare mechanisms (recurrent timing nets) that would produce similar kinds of behaviors. What is needed is a mechanism that both builds up an expectancy of patterns of events when they recur, and computes the deviation of the incoming stream of new events from what was expected at that particular time point.

There is an ongoing debate about the nature and meaning of the MMN [56]. Some current theories of the MMN hold that a memory trace is formed when the standard is repeated and that there is a comparison of incoming neural activity patterns against this memory trace that was constructed from very recent experience. Others hold that the memory trace itself may be embedded in the responses of ensembles of cortical neurons. Still others reject the notion of organized memory traces in favor of explaining the MMN in terms of neuronal adaptation processes.

It is notable that early studies of electrical conditioning in single neurons, conducted before MMN was discovered, found that cortical neurons assimilated rhythmic patterns (10 Hz flashes of light) that were presented in conjunction with correlated electrical pulses similar in many respects to a reward signal [34, 57, 58]. The stimuli were presented over and over, paired with electrical pulses; and over tens of trials the temporal response pattern of the neurons came to resemble that of the stimulus (10 Hz firing pattern). When the stimulus was then abruptly changed to 1 Hz, the slower flashes evoked the 10 Hz pattern for many repetitions, but eventually the assimilated rhythm was extinguished.

3.4 Temporal Theories of Associative Memory

Predictive timing is a key element of anticipatory behavior. It is often important to know when a reward will come. The relative timing of rewards and the events that lead up to them has been an ongoing concern of theories of learning.

It has also been observed that spike timings of dopaminergic neurons reflect discrepancies between anticipated and observed courses of the neural concomitants of events associated with rewards [59, 60]. This discovery has spawned a host of adaptive temporal prediction models.

Many studies in animal and human conditioning suggest that the timings of all correlated events relative to the arrival of a reward are implicitly and intrinsically stored in both short and long term memory, such that any of them can serve as anticipatory temporal predictors [61]. This temporal coding of memory hypothesis thus proposes that “the temporal conditions (e.g. the CS-US interstimulus interval) are not merely catalysts in the formation of associations, but are also a part of the content of learning” [62]. The hypothesis further asserts that animals can build temporal maps from relationships between events that were never physically paired, “that is, temporal information from different training situations which have a common element can be integrated based on super-positioning of the common element in different temporal maps” [63]. This means that systematic maps of temporal relations between events can be built up from separate experiences of subsets of events. Such maps of temporal relations can then subserve anticipatory prediction—each event becomes a predictor for other temporally correlated events [64].

4 A Temporal Theory of Brain Function

Brains implement anticipatory predictions that subsequently guide behavior. In this paper we propose a high-level theory of brain function based on temporal pulse pattern codes that can be actively regenerated, stored, and retrieved. In this theory, prediction and steering of behavior are achieved by encoding and retrieving temporal patterns of spikes associated with internal events connected to percepts, actions, rewards, and punishments. Although it shares many assumptions with mainstream connectionist theory, (e.g., recurrent connections, distributed coding and processing), this proposed theory differs from connectionism in its fundamental neural coding assumptions. Whereas connectionism is based entirely on channel-activation codes (which neurons fire at which average rates), the alternative neural architectures envisioned here rely on temporal codes, i.e., neural codes that encode distinctions in temporal patterns of spikes.

A general theory of brain function requires specification of several basic aspects.

1. *Neural codes*. What are the system's signals? A neural coding scheme based on spike timing patterns must be capable of representing all the distinctions that we make (e.g., encoding all of the attributes of objects, events, and their relations and their compositions).
2. *Neural networks*. What processing architectures are needed to realize the informational signal processing operations that the system performs? A neural processing architecture capable of operating on temporal patterns in order to carry out informational operations—such as detections, discriminations, pattern recognitions, invariances, transformations, and groupings—is required.
3. *Memory mechanisms*. How are informational distinctions encoded and decoded in memory? Here mechanisms of short- and long-term memory that can store and recall temporally coded temporal patterns in a content-addressable manner are needed.

These different aspects of the system need to be compatible with each other. The nature of the neural codes that bear informational distinctions heavily determines the nature of neural signal processing architectures and the memory mechanisms needed to utilize them. Conversely, the available neural mechanisms for processing, storing, and retrieving information heavily constrain what kinds of codes the system can use.

5 A Universal Coding Framework Based on Complex Temporal Spike Patterns

5.1 The Neural Coding Problem

Understanding the nature of the neural code (the "neural coding problem") in central circuits is arguably the most fundamental problem facing neuroscience today. Without an understanding of the precise nature of the "signals of the system," we cannot have a firm grasp of the nature of information processing and storage in brains. Neuroscience today is in a situation comparable to cellular biology and genetics before DNA nucleotide sequences came to be understood as the primary vehicle for inheriting and expressing genetic information. However, neural coding is rarely explicitly mentioned as an unsolved problem in neuroscience. Although interest in neural coding has undergone cyclical changes from decade to decade, it has never yet risen to the forefront of neuroscience.

A common tacit assumption in mainstream neuroscience is that the coding problem has already been solved, that the brain is a large, complex connectionist network. The instantaneous functional states of the system are thought to be patterns of average firing rates across neurons, and its structural informational states are thought to be characterizable in terms of interneural connection weights. The instantaneous functional state (mental state), taken together with the structural state (the "connectome"), is thought to determine how the system behaves. Note that these assumptions only hold to the extent that spike timing and temporal relations between neurons (intra- and inter-neuronal time delays) have no significant role in informational functions. Solving the neural coding problem is critical for interpreting the functional significance of specific neuronal connection patterns.

Neural codes, as discussed here, are the functional signals of the system, those neuronal activity patterns that have functional significance for information processing in the brain. Different kinds of informational distinctions (e.g., perceptual attributes, thoughts, desires, affective states) and their specific alternatives (e.g., for the visual attribute of color, the distinctions of red vs. blue vs. green vs. yellow) are mediated through specific patterns of neural spiking activity. These specific types of patterns and different patterns within a type constitute the neural codes [65–69].[4]

This notion of coding is related to the conception of a sign in semiotics as a distinction that has functional significance for its user. A sign, in Gregory Bateson's phrase, is a "difference that make a difference." A neural code is a pattern of activity that makes a functional difference in the brain, i.e. a difference that alters internal functional states and subsequent behavior. To go further, some spike patterns may be meaningful, having consequences for internal states or overt behaviors, whereas others that are not interpretable within a coding scheme may not constitute a coherent internal message, and so would not be meaningful to the system. Examples of the latter might include uncorrelated "spontaneous" spike patterns, spikes generated during epileptic seizures, and incoherent firing patterns produced under general anesthesia.

5.2 Types of Neural Codes: Channel Codes and Temporal Codes

Neural pulse codes can be divided into two types: channel codes and temporal codes. In channel codes, activation of particular subsets of neurons (channels)

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[4] The functional definition of neural coding is different from formal, information-theoretic Shannonian estimates of channel capacities that are independent of whether or not the system makes use of the different states.

conveys distinctions (e.g., through across-neuron firing rate profiles), whereas in temporal codes particular temporal patterns of spikes convey distinctions. Temporal codes can be further divided into those codes that depend on temporal patterns of spikes irrespective of their times-of-arrival (spike latency) and those codes that depend on the relative latencies of spikes. Temporal pattern codes based on inter-spike intervals appear to subserve auditory pitch and cutaneous flutter-vibration sensations, whereas relative time-of-arrival codes appear to subserve various stimulus localization mechanisms based on temporal cross-correlation in audition, somatoception, and electroception.

Connectionist theory adopts the assumption that the central codes operant in brains are firing-rate channel codes, whereas the neural timing net theory outlined here posits that these are complex temporal pattern codes. Thus, for most of the history of modern neuroscience, channel coding has been adopted as the conventional, default assumption and with it, connectionism as the default neural network assumption. However, a significant minority opinion has involved proposal of various kinds of temporal codes as alternatives [65]. Early examples include Rutherford's "telephone theory of neural coding," Troland's temporal modulation theory of hearing, Wever's temporal volley theory, the Jeffress' model for binaural localization, and Licklider's duplex model for pitch perception. There has likewise always been an alternative tradition for temporal processing architectures as well [70–74]. We have discussed many of these various neural coding schemes elsewhere [69, 75, 76].

5.2.1 Types of Temporal Codes

In simple temporal codes (Fig. 5a), one temporal parameter conveys one perceptual distinction. For example, in the early auditory system, times between spikes (interspike intervals) carry information about the periodicities of sounds. At these early auditory stations, the neural code for pitch involves the mass statistics of interspike intervals amongst whole populations of neurons [49, 69, 79]. The pitch that is heard corresponds to the most common interspike intervals that are produced by the population. The sensation of flutter-vibration has a similar basis in simple interspike interval patterns. Binaural auditory localization in the horizontal plane utilizes sub-millisecond spike timing differences produced by corresponding neurons in neural pathways that originate in the two ears. Analogous examples exist in nearly every sense modality [76].

Complex temporal pattern codes can be formed from combinations of simple temporal-pattern primitives (Fig. 5a–c). Here different orthogonal *types* of temporal patterns encode different independent primitive features. For example, for a musical note-event, the different dimensions of pitch, loudness, duration, location, and tonal qualities (timbral distinctions) would be conveyed via different types of temporal patterns of spikes that were produced concurrently within some population of auditory neurons (Fig. 5c). Combinations of specific temporal patterns present at any given time form a feature-vector whose dimensions are determined by the pattern types.

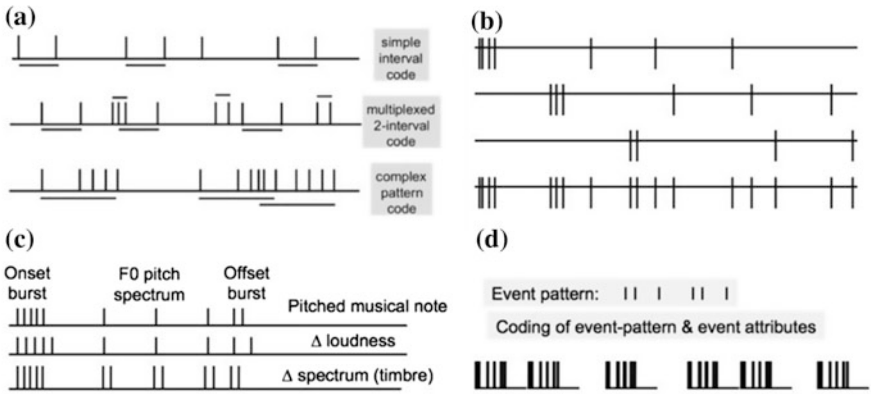

Fig. 5 Temporal codes. Idealized spike trains illustrate different coding schemes. **a** Simple and complex temporal pattern codes: *top* interspike interval code (e.g., for pitch or flutter-vibration); *middle* multiplexing of two different interspike intervals related to different types of information; *bottom* complex pulse pattern code. **b** Multiplexing of three complex temporal patterns associated with different types of cutaneous sensation (after [76]); *bottom* spike train shows interleaving of the different signals. **c** Hypothetical spike latency pattern scheme for encoding different attributes of auditory events (pitch, loudness, timbre, duration). **d** Hypothetical universal scheme for encoding event-patterns that includes event attributes and the relative timings of events

Complex temporal codes can potentially be conveyed in single units or in the pattern-statistics of spike time patterns in ensembles and populations. The various patterns can be interleaved or embedded in other patterns of spikes (Fig. 5b), permitting signal multiplexing (concurrent transmission of multiple types of signals over the same neuronal transmission lines). A complex temporal coding scheme that was proposed in the past for multiple cutaneous sensory qualities [78] provides a concrete example of how such codes might be organized.[5]

A neural code must convey two types of information: the type of distinction the signal conveys (e.g., pitch or color), and the attribute distinction itself (e.g., a particular pitch or color). In channel codes, the identity of the channel (which neuron, as determined by its place in the network, its interconnectivities) conveys informational type, whereas patterns of channel activations convey different attribute values. For channel-coding schemes, neural channel-identities maintained via specific interconnections are absolutely critical for function. A neural firing rate is meaningless to the rest of the system without the identity of the neuron that is firing. Connectionist networks are completely dependent on the maintenance of highly regulated connectivities ("synaptic weights").

In contrast, because complex temporal codes embed the type of the signal in the form of the message, highly specific interneural connectivities and signal transmission paths are no longer essential for function. Temporal codes thus permit

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[5] As far as we know, Emmers' findings have not been replicated experimentally by others, so the neuronal reality of this powerful, multidimensional coding scheme is unproven.

"signals to be liberated from wires." As long as the patterns can propagate to other populations, the specific paths they take does not change the nature of the messages sent. Thus this mode of neural communication enables broadcast modes of signal distribution. Neuronal assemblies downstream can be selectively tuned such that they respond to particular temporal patterns embedded in their inputs. Broadcast, multiplexing, and selective tuning enable decentralized communications in which tuned neural assemblies can respond only to those incoming signal patterns that are relevant to their functional roles. Here a "neural assembly" is used in the Hebb-Lashley sense of a functional organization of a set of neurons—a given neuron may participate in many different neural assemblies that are organized around different tasks [80]. Some codes may be restricted to local neuronal populations (e.g., restricted cortical regions) that handle specific types of information, whereas others may be propagated more globally, re-broadcast by the hippocampus, and then consolidated into long term memory.

Finally, complex temporal codes can represent patterns of events that occur over different time scales. If a sequence of musical notes is played, such as a motif or a melody, a temporal code that can encode all of the attributes associated with the individual events can also encode the timings of the events (Fig. 5e). Thus rhythmic pattern and musical meter can be encoded on coarser timescales and the same coding framework can handle different levels of musical organization.

5.2.2 Evidence for Temporal Codes

Temporal codes are found in a very wide range of sensory systems [66–69, 75–79]. Temporal codes in sensory systems have been found with sub-microsecond spike timing precisions (electroception), microsecond precisions (bat and cetacean echolocation), sub-millisecond precisions (auditory, somatoception, vision), and still coarser (olfaction, gustation).

Generally speaking, auditory systems tend to have the highest frequencies of the synchronization of spikes with stimuli. In the auditory systems of barn owls, who use spike timing to localize their prey in the dark, spikes fire in time with the fine structure of sounds up to periodicities of 10 kHz. In humans and cats, primary auditory neurons phase lock up to roughly 5 kHz. Next, spike synchronizations to electrical shocks delivered to the skin approach rates up to about 1 kHz. Visual neurons lock to modulations in luminance up to roughly 100 Hz.

Temporal codes are found not only in sensory systems in which spikes follow the fine time structure of the stimulus, such as hearing and touch, but also in sensory systems such as vision, where eye movement transforms spatial luminance patterns into correlated temporal patterns at the retina. Even in the chemical senses of smell and taste, and in color vision, differences in the temporal response properties of sensory receptors produce corresponding characteristic temporal patterns of spiking.

In general, the most obvious temporal codes are found near sensory receptor surfaces. In early stations of the auditory system, spike timing is most abundant and its functional role most obvious. However, as one proceeds up ascending sensory pathways, stimulus-related timing information is mixed with other kinds of information and in some cases smeared out such that stimulus-related fine timing information above roughly 100 Hz becomes successively less apparent as one proceeds to the cortical level [75]. In the auditory system, despite considerable progress, cortical representations for basic auditory attributes such as pitch and loudness are still poorly understood [81].

In lieu of strong coding hypotheses, it is difficult either to confirm or entirely rule out prospective candidate codes at the cortical level. Thus the complex temporal pattern-coding scheme outlined here is a very tentative hypothesis. If complex temporal codes do exist in central circuits that subserve the representation of all simple sensory attributes associated with events (e.g., the timing, duration, loudness, pitch, and timbre of a single musical note), they may involve timing patterns that are difficult to observe because they are distributed across neurons and/or not rigidly synchronized either with the stimulus or each other.

Although temporal patterns associated with fine temporal structure above a few hundred Hz are not abundant at the cortical level, temporal patterns of neuronal response associated with the slower successions of onsets and offsets of discrete sensory and motor events (periodicities <10 Hz) are very prominent. The precision of the coding of these onsets, on the order of 100–200 μs, is maintained all the way up the auditory pathway. Temporal patterns related to patterns of musical events, flashing lights, electric shocks, and tactile pulses are widely observed in evoked electrical and magnetic activity over large parts of the cerebral cortex [34, 46].

Musical rhythm is thus a prime candidate for temporal coding. Patterns of event onsets are seen widely in averaged electrical and magnetic auditory evoked potentials and also more recently even in single trial stimulus presentations. At present, it is possible to determine which of two auditory streams a listener is attending on the basis of the corresponding rhythmic pattern of neuronal response in an EEG or MEG signal. Even beats that are expected, but not presented or heard, as in a syncopated meter, produce observable responses at the times when the acoustically sounded beat was expected to arrive [82–84]. Actively imagining a rhythmic pattern facilitates the pattern in neuronal cortical populations such that it can be observed in EEG recordings.

Rhythms in speech, though less regular and not as well defined as their counterparts in music, likewise produce corresponding temporal patterns that reflect acoustic contrasts [52, 85]. Recently rhythmic patterns of neuronal response associated with different levels of sentential organization (e.g., syllables, words, phrases, sentences) have been observed at the cortical level [86].

All of these phenomena argue for direct temporal coding of rhythm in music and speech at all levels of auditory processing. Coarse rhythmic patterns (<10 Hz) are supra-modal, with neural temporal responses that are very widely distributed across cortical regions [46]. The ubiquity of these correlated neural response patterns may explain how musical rhythm can provide a cross-modal temporal scaffold for movement and memory [87].

In the last decade, there has been a renewed interest in brain rhythms, and many of these phenomena have been interpreted in terms of oscillatory dynamics of neuronal populations [86, 87–89], rather than under the rubric of temporal codes [49, 51, 90]. It is important to distinguish between evoked, exogenous rhythms that reflect driving stimulus periodicities both from endogenous rhythms produced by intrinsic dynamics of neuronal excitation and recovery and from induced rhythms that are triggered or released by external stimulus events. The focus is usually on entrainment and induced rhythms rather than stimulus-locked synchronization or stimulus-related periodicities. Synchronization is often regarded as a passive process, in contrast to "active modification of ongoing brain activity" in entrainment [51]. Note, however, that for every observed oscillation, there is an associated temporal organization of spiking activity. Recent evidence points to substantial functional roles for both evoked and induced rhythms in the grouping and analysis of speech and musical events. Oscillatory dynamics of cortical neurons may govern temporal processing windows for music and speech [89, 91, 92] in a manner that limits the rate at which events and their various attributes can be accurately represented. In terms of neural coding, the durations of these windows may place constraints on how fast complex spike latency codes (such as the code of Fig. 5c), which require different readout times for different attributes, can be produced and processed.

6 Neural Architectures for Temporal Processing

What kinds of neural architectures would be needed to utilize a temporal coding framework such as the one outlined above?

6.1 Basic Plan of the Brain

The basic structural plan of animal brains [93] is well-conserved phylogenetically. Despite its apparent neuroanatomical complexity, brains consist of a relatively small number of component subsystems and neuro-computational architectures. First and foremost, as neuroscientists have understood for more than a century now, the brain is a network of recurrent pathways. These have variously been called loops, neural circuits, re-entrant paths, and nets with circles.

The brain can thus be regarded as a network of neuronal circuits, i.e., large numbers of interconnected neuronal loops that contain excitatory and inhibitory neurons with local connections, and excitatory (and sometimes inhibitory) neurons with longer range projections. Many different canonical neural circuits have this recurrent organization (e.g., thalamocortical loops, cortico-cortico re-entrant pathways, and hippocampal loops). The systematic sets of recurrent pathways in the hippocampus have been often regarded as computational substrates for an auto-associative memory mechanism. Different regions of the cerebral cortex are reciprocally connected to neighboring ones by local connections and to more distant cortical regions by white-matter long-range axonal tracts. However, closed cyclical chains of excitatory neurons without inhibition create positive feedback loops that quickly saturate. By regulating the amount of inhibition, the loop-gains of these circuits can be modulated from their resting, slightly attenuating state, in which incoming neuronal activity patterns die out, to states of attention.

For the most part, neuroscience has been more focused on the neuroanatomy of connections, i.e., "the connectome," than on temporal relations within and between the various neuronal populations. However, for timing theories of brain function, each connection between neural elements has not only a synaptic weight, but also time delays associated with axonal and synaptic transmission. Each of these various loops have characteristic time delays associated with them: short-delays for local circuits and longer ones amongst more distant neuronal ensembles. The more numerous unmyelinated axons, with their slow conduction velocities and long conduction times, yield much longer transmission delays than myelinated axons. In addition, there are delay processes that are inherent in the recovery dynamics of the neuronal elements that can perform many of the same neural signal processing functions as transmission delays.

6.2 Neural Time-Delay Architectures

Purely connectionist networks do not represent time explicitly, except as sequences of changing spike rates. Time-delay networks, on the other hand, include time delays between elements that allow them to interconvert temporal patterns and spatial activation patterns. Early time-delay neuro-computational architectures were proposed for that utilized binaural time disparities for localizing sounds and monaural interspike intervals for perceiving periodicity pitches (Jeffress and Licklider models, [52, 59]).

Time-delay networks use coincidence-detector elements with short time integration windows for handling temporal patterns of spikes, and rate-integrator elements with long time integration windows for converting spike coincidences to average firing rates. This "coincidence counting" allows them to interface with connectionist architectures. In effect, temporal codes are converted to rate-channel codes. Time-delay architectures can be flexible in their ability to handle both temporal and spatial information: by tuning delays, one can change synaptic efficacies, and vice-versa.

6.3 Neural Timing Network Architectures

After many years of searching for alternatives to both connectionist rate-place and time-delay neural network schemes, I proposed yet a third kind of neural network, which I called *neural timing nets*. For the most part, early work on these networks involved demonstrating the various time-domain operations that could be elegantly carried out [94–96].

Temporal pattern codes allow simple form transformations (position shift invariance), and time warping of patterns yields tempo-invariance of rhythms, transposition invariance of pitch sequences, and magnification invariance of spatial forms. Using these kinds of temporal representations, separation of independently moving or changing forms can be effected. One can easily separate objects on the basis of invariant relational patterns of elements within objects (fusion, grouping) vs. the changing relations between elements of different, independently moving objects (separation).

Neural timing networks consist of arrays of delays and coincidence elements that operate on temporally-coded inputs and produce temporally coded outputs. Essentially, everything is kept in the time domain, and neural signals can interact with each other to sort out common temporal subpatterns. Whereas connectionist and most time-delay architectures are “connection-centric” (all informational function depends on particular synaptic connection weightings), neural timing networks are “signal-centric” (action lies in interactions between signals: “signal dynamics”).

The signal-centric nature of the networks (and networks processing based on signal dynamics) sidesteps many of the problems of connectionist and time-delay network architectures, in that precise and elaborate point-to-point connections are not needed for such networks to function. It is enough to bring the various neural signals into the same regions at approximately the same time. By operating on the temporal pattern statistics of ensembles of neurons, as long as there are some points of interaction, it no longer matters whether this or that neuron produced this or that output.

Feedforward timing nets (FFTNs) are arrays of coincidence detectors and delay lines that cause temporally patterned signals to interact. Various correlation and convolutional operations can be carried out, enabling multiplexing and demulitplexing of signal primitives. In FFTNs the spike train signals collide, interact, interfere, and/or mutually amplify each other, essentially performing correlation-like filtering signal processing operations in the time domain.

Compared to connectionist networks, the temporally coded representations and signal processing operations are more iconic and analog in character and more parallel in implementation. Template matching can be realized by injecting a temporal pattern archetype into the network, which will serve to amplify any incoming temporal pattern signals that have significant correlations with it. Content-addressable search can likewise be realized by injecting temporal patterns related to the features that one is interested in. Other neural signals circulating within the network will interact with the search signal if and only if they have feature-related temporal subpatterns in common. Essentially complex temporal pattern signals can implement a vectorial representation in which the signals themselves can sort out those dimensions that they have in common. The informational operations involve “pattern resonances” [97]. The processing scheme as it currently stands is provisional and still in a rudimentary state of development.

Nonetheless, it appears to be much more flexible than any connectionist scheme we have seen to date.

7 Temporal Mechanisms for Short-Term Regenerative Memory

Most high level accounts of brain function posit networks of recurrent pathways (re-entrant loops, neural circuits) that support a dynamic, working short-term memory coupled to a more permanent long-term memory mechanism that permits storage and retrieval of relevant patterns (Fig. 2). Neuronal activity patterns that have hedonic salience for the animal (i.e., are part of a string of events that leads to significant reward or punishment) are rebroadcast by the hippocampal formation such that the patterns are maintained in working memory and later consolidated and fixed in long-term memory. This rebroadcast can replicate event sequences at faster-than-real-time rates.

Conventionally, the nature of short-term memory is commonly assumed to involve subsets of specific neurons in recurrent neural circuits that maintain higher rates of activity, whereas long-term memory is thought to involve changes in the effective connectivities between neurons at synapses (in neural network terms, “synaptic weights”). Thus short-term memory is conceived in terms of a complex reverberation pattern of neuronal activations, while long-term memory is thought to entail more permanent synaptic changes.

In addition to feedforward timing nets, there also can be recurrent timing nets (RTNs), in which there are arrays of delay loops that span a wide range of recurrence times. RTNs were initially conceived as models for pitch- and rhythm-based grouping and separation mechanisms [94–96]. For both pitch and rhythm, repeating waveforms and temporal event patterns respectively create strong temporal expectancies and groupings. Our auditory systems easily separate concurrent sounds with different fundamental frequencies (F0 s), such that we are able to hear out different musical instruments and voices when they are mixed together. RTNs, which act in a manner similar to adaptive comb filters, separate out the respective temporal patterns of multiple speakers with different voice pitches and of multiple musical instruments playing different notes.

Recurrent timing nets are perhaps the simplest kind of reverberating, temporal memory that can be imagined (Fig. 6a). Here an incoming pattern is compared with a delayed circulating pattern; and if the recurrence time of the delay loop is equal to the repetition time of a repeating pattern, then the pattern is facilitated (builds up) in that particular loop. If the difference between the circulating and the incoming pattern is also computed, then the difference signal can be fed into the array. Each delay loop creates an expectation of what the next incoming signal fragment will be. (The expectation is a primitive anticipation in that the recent past is used to predict the near future.) In the case of a repeating pattern of auditory events, each

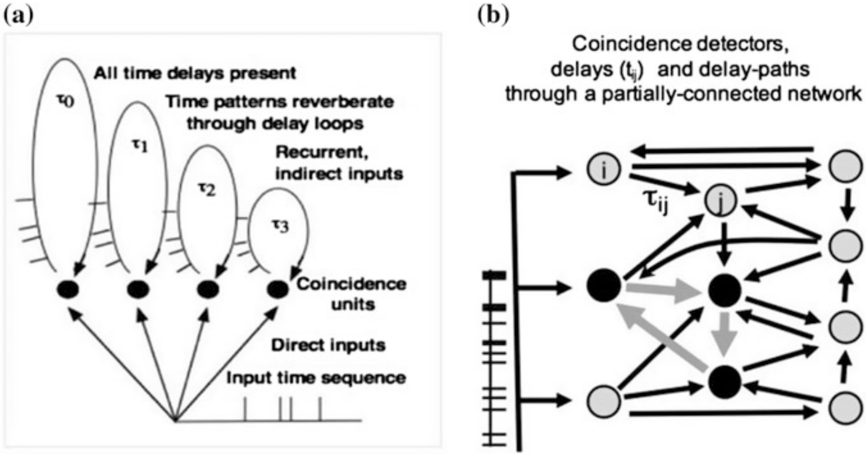

Fig. 6 Recurrent timing nets (RTNs). **a** An array of delay loops and correlation-facilitated coincidence detectors. A periodic pulse pattern fed into the network maximally facilitates itself in the delay loop, whose recurrence time is equal to the duration of the repeated pulse pattern, not unlike a time-domain implementation of a comb filter. Such a network stores temporal patterns in the delay loops. Multiple periodic patterns sort themselves out in the different delay loops, which then function as complex pulse pattern-oscillators. **b** Alternative implementation of a neural timing net in a richly interconnected network of coincidence-facilitating elements. A pulse pattern is fed into the leftmost, input layer and delay paths corresponding to the internal delay structure of the stimulus are facilitated (*gray arrows*, *black coincidence elements*). The reverberating patterns are regenerated within the network (synfire cycles)

delay loop is making a temporal prediction about when the next event will occur. And if the event-attributes (timing, loudness, pitch, timbre, duration, location) are also encoded in time via a complex, multidimensional time code, then it creates expectancies for those also.

The RTN delays can be either monosynaptic (recurrent collaterals) or polysynaptic (delay paths through networks, Fig. 6b). The number of recurrent monosynaptic 2-element paths in a fully connected network of N elements is on the order of N^2. The number of paths increases combinatorially with maximum path-length M, roughly as M^N. Although the brain is thought to be more like a small world rather than a fully interconnected network [98], all neurons are thought to be interconnected by at most three or four interneurons. The number of delay paths is still astronomical, far greater than even the combinatorics of individual synapses (because each synapse connecting two neurons has a delay associated with it).

If the synapses are spike-timing dependent (inhibited/facilitated by recent spike correlation history), then the repeating pattern will flow through those delay-paths that have recurrence times equal to the pattern repetition time. Other paths with other delays that are not in the pattern will be temporarily inhibited. In this manner, to whatever degree there is repetition, the recurring time structure of the rhythm input will build up in the network. If there are only locally repeating patterns, say ABCABCCABBCDEFAB, which has a maximum repeated pattern length of 2 (AB), then the network will revert to the probabilities of shorter sequences. This becomes a neural implementation of a variable-order Markov chain that can adapt to variable N-gram lengths. The system thus predicts specific, longer sequences when those have been presented in the not-too-distant past, but in lieu of repeating sequences reverts to Bayesian statistics.

Timing-dependent synapses support competition between signals and winner-take-all dynamics (facilitation of one set of signals inhibits others), as well as the possibility of regenerative, self-facilitating “synfire cycles.” These differ from synfire chains [73, 99, 100] in that the temporal pattern statistics, rather than which neurons are firing, encode particular attribute distinctions. The regenerative cycles in effect would constitute a temporal echoic and working memory buffer that would hold the temporal patterns (maintaining the statistics of the patterns) such that they could be compared with incoming ones.

8 Temporal Mechanisms for Long-Term Memory

Lastly, a general theory of brain function needs to account for a second memory mechanism by which permanent, stable long-term memories are laid down and their contents retrieved. The nature of the storage mechanisms operant in brains, Lashley’s “engram” [80], is a fundamental problem that is intimately related to the neural coding problem. The competing theories of memory parallel those of neural coding and neural architectures [34, 101].

As Lorente observed, “permanent circulation of impulses in neural chains” cannot be the basis for long-term memory because these memory traces survive the cessation of neuronal activity that occurs under anesthesia, deep shock, and hibernation [102]. Like short-term memory, long-term memory is content-addressable. Neuronal activity associated with any attribute can be used to activate long-term memory traces that encode that attribute. Two alternative types of temporal long-term memory mechanisms can be envisioned that could store and retrieve events encoded via complex temporal spike patterns.

8.1 Formation of Time-Delay Networks for Recognizing and Producing Temporal Patterns

The first possibility tunes up time-delay networks to produce the complex temporal patterns that are to be stored. First the temporal patterns are repetitively presented to neuronal populations such that synapses with offsetting time delays that produce spike-timing correlations within the local network are strengthened via spike-timing-dependent plasticity (STDP). The result would be that the repetitive complex patterns presented to the network would be assimilated in a manner similar to what was observed under the electrical conditioning experiments discussed earlier [58]. Subsequent activation of such a network might reproduce the consolidated delay pattern, thereby recreating the stored complex temporal pattern and injecting it into the rest of the network such that it can interact with signals that are currently circulating in regenerative short-term memory.

This explanation has the merit of relying on the same kinds of synaptic changes as connectionist theory. There is a great deal of accumulated biophysical evidence of semi-permanent changes in synaptic efficacy with use, and this process could involve those mechanisms. In effect, the neuronal assemblies become time-delay networks that are configured from past experience. These can become activated by incoming temporal patterns to facilitate channel activations (connectionist account) and/or to emit temporal patterns (timing net account).

8.2 Polymer-Based Time-Space Molecular Memory for Storing Temporal Patterns

A second possibility is that of a molecular memory that stores time patterns. Molecular memory mechanisms have been discussed for some time [103], and many are inspired by the power of the genetic nucleotide sequence code. A temporal molecular memory is attractive because it does not depend on particular, highly specific synaptic connections. Theories of RNA-based molecular memory ("memory RNA") that were inspired by planaria memory transfer experiments were popular in the early 1960s, but due to failures to clearly replicate the basic transfer phenomena, this entire field was defunded at the NIH for a generation. In recent years, research on possible molecular memory mechanisms has been revived [64].

Complex temporal patterns lend themselves to instructional "tape recorder" memory mechanisms [33, 101, 104] that preserve temporal relations between events. If the attributes of the events are also temporally coded (e.g., sensory features of a particular place in a maze), then such temporal memory traces can serve as universal memory mechanisms whose form need not be radically transformed in the storage and retrieval process. I have previously proposed a mechanism similar to the scheme in Fig. 7 [105].

One potential molecular mechanism is that time patterns of intracellular ionic fluxes could be converted to spatial patterns of markers on polymers [106]. We

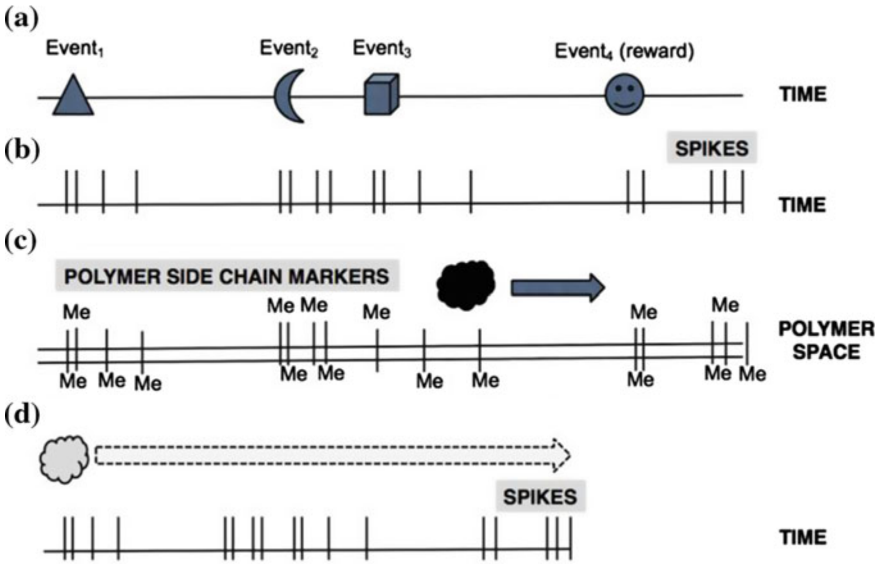

Fig. 7 Hypothetical scheme for long-term molecular storage of temporal patterns. **a** A sequence of temporally correlated events (1–3) that lead to a reward event (4). **b** Internal spike patterns produced by the internal events (e.g., encoding event-feature attributes). **c** Polymer (*double lines*) consisting of a backbone chain plus side-chains that can be chemically modified (e.g. methylated). A polymerase moves along the polymer backbone, adding a side-chain marker whenever the neuron is depolarized (or ionic concentrations change). The polymerase moves at a constant speed down the chain, thereby converting temporal pulse patterns to spatial patterns of markers on the polymer. **d** A second type of polymerase that moves down the chain at a faster rate, triggering ionic fluxes and generation of action potentials when a marked side chain is encountered. Such a mechanism would enable faster-than-real time readout that could subserve anticipatory steering of action

know that there are polymerases that move down the length of polymers, presumably at a constant average speed, and that there are also mechanisms for reversibly labeling the side chains of these polymers (e.g., methylation). Thus it is conceivable that temporal patterns of ionic fluxes (e.g., related to local calcium concentrations) could be laid down along the length of a polymer by a writing enzyme (there are much higher concentrations of DNA methylase in the nervous system than in other tissues). A second reading polymerase could scan the polymer at the same (or even faster) rate than the writing enzyme, thereby reading out the pattern. If all neural information related to relative event timings, attributes, and resulting reward or punishment is stored, as conditioning studies suggest, then a faster-than-real-time readout mechanism becomes a relatively simple means of predicting the future hedonic consequences (reward or punishment) of a present situation or course of action.

9 Conclusions

A theory of brain function based on complex temporal pattern spike codes, neural timing net architectures, and temporal memory mechanisms is outlined. Short-term temporal pattern memory entails regeneration of complex temporal patterns of spikes, whereas long-term temporal pattern memory could involve either tuning of time-delay networks or a polymer-based time-space molecular mechanism.

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