

Neural Syntax: Cell Assemblies, Synapsembles, and Readers

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A widely discussed hypothesis in neuroscience is that transiently active ensembles of neurons, known as “cell assemblies,” underlie numerous operations of the brain, from encoding memories to reasoning. However, the mechanisms responsible for the formation and disbanding of cell assemblies and temporal evolution of cell assembly sequences are not well understood. I introduce and review three interconnected topics, which could facilitate progress in defining cell assemblies, identifying their neuronal organization, and revealing causal relationships between assembly organization and behavior. First, I hypothesize that cell assemblies are best understood in light of their output product, as detected by “reader-actuator” mechanisms. Second, I suggest that the hierarchical organization of cell assemblies may be regarded as a neural syntax. Third, constituents of the neural syntax are linked together by dynamically changing constellations of synaptic weights (“synapsembles”). The existing support for this tripartite framework is reviewed and strategies for experimental testing of its predictions are discussed.

“If a tree falls in a forest and no one is around to hear it, does it make a sound?” – Attributed to George Berkeley¹

Introduction

Donald Hebb was among the first thinkers who explicitly stated that the brain's ability to generate coherent thoughts derives from the spatiotemporal orchestration of neuronal activity (Hebb, 1949). Hebb hypothesized that a discrete, strongly interconnected group of active neurons, the “cell assembly,” represents a distinct cognitive entity. Because of their high interconnectivity, the stimulation of a sufficient number of assembly members can activate the entire assembly (Legendy, 1967; Palm, 1982, 1987). The chaining of such assemblies by some internal mechanisms (Hebb's “phase sequences”), in turn, would provide the basis by which complex cognitive processes, such as memory recall, thinking, planning, and decision making, could flow independently of direct control from the environment or the body (Churchland and Sejnowski, 1992; Harris, 2005; John, 1967; Kelso, 1997; Laurent, 1999; Palm, 1982; Pouget et al., 2000; Pulvermüller, 2003; Sakurai, 1999; Singer, 1990; Varela, 1995; Varela et al., 2001; Wickelgren, 1999; Yuste et al., 2005). With Hebb's cell assembly hypothesis, it appeared that cognitive neuroscience had established a comprehensive research program to link psychological and physiological processes. The expectation was that the program would demonstrate that (1) the spiking activity of a strongly connected collection of neurons is the basic unit for neuronal coding and (2) activation of a (sufficiently large) part of the assembly can reconstitute activity in the entire cell assembly, similar to our subjective ability to reconstruct wholes from fragments. However, experimental identification of the hypothesized cell assemblies has proven notoriously difficult (Gerstein et al., 1989; Grossberg, 1969; Ikegaya et al., 2004; Lansner, 2009;

Milner, 1957, 1996; Palm, 1982, 1987; Pouget et al., 2000; Pulvermüller, 2003; Singer, 1999; Wallace and Kerr, 2010; Wennemers et al., 2003). For the past several decades, the limitations were primarily technical, namely, the lack of appropriate methods to record simultaneously from large enough numbers of neurons in behaving animals (Abeles, 1991; Strangman, 1996; Edelman, 1987; Hebb, 1949; Palm, 1982). However, the recent rapid progress in large-scale recording of individual neurons in multiple brain regions (Buzsáki, 2004; Buzsáki et al., 1992; Eichenbaum and Davis, 1998; Nicolelis, 1999; Wilson and McNaughton, 1993) and the initial attempts to track down and experimentally define putative cell assemblies (Harris et al., 2003; Harris, 2005; Truccolo et al., 2010) led to the recognition of another level of difficulties of a more conceptual nature.

How large is a cell assembly, what is its duration (“lifetime”), and what, exactly, does it represent in the cognitive or output domain? Does an assembly represent a feature, a figure or background, an object or concept, a thought process, a plan for immediate action, or even more complex processes?² (This and other notes are explicated in the Supplemental Information available online.) Unfortunately, the very idea of identifying the neuronal correlates of such psychological constructs on the presumption that they must have clear boundaries, in correspondence with the neuronal substrates of their representation, is questionable. According to the “representational framework” (Engel et al., 2001; Hebb, 1949; James, 1890; Milner, 1996; von der Malsburg, 1994), the way to identify cell assemblies is to present various stimuli to the brain (e.g., an object or aspects of an object) and examine the spatiotemporal distribution of the evoked neuronal responses (Hubel and Wiesel, 1962; Rieke et al., 1997).³ An implicit goal of such a strategy is to eventually explain how elementary attributes that are believed to comprise an object (e.g., color, shape, odor, sound, motion, etc.) are bound together at the neuronal level so that the object is

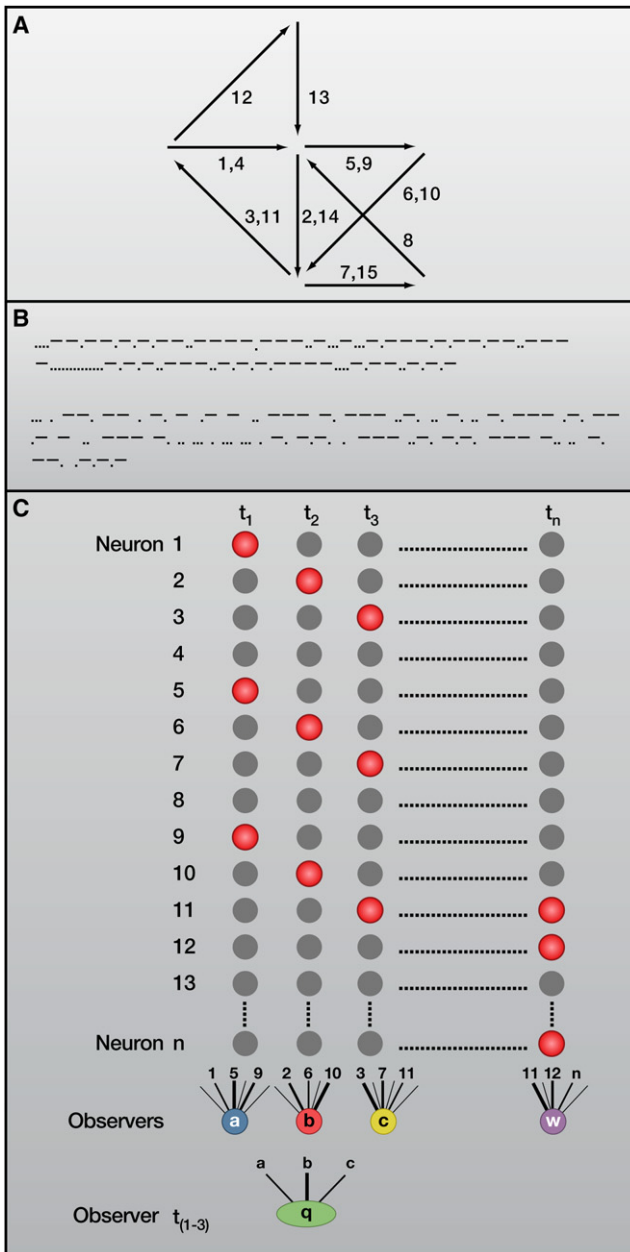


Figure 1. Cell Assembly and Assembly Sequences

(A) Hebb's reverberating cell assembly sequences ("assembly phases"; modified with permission after Figure 10 of Hebb, 1949). Arrows represent transitions between individual assemblies. The direction of activity flow across assemblies (edges) is determined by the stronger synaptic strengths among assembly members relative to other connections (not shown). The same assembly can participate in a sequence more than once (e.g., pathway 1, 4 indicates recurring transitions). No mechanism is postulated to explain why activity does not spread to all parts of the network and reverberate forever.

(B) Top: long sequence of two characters (e.g., dot and dash). Its embedded information is virtually impossible to recover. Bottom: same exact sequence as above after adding syntactic segmentation (space = stop-start punctuation) between the short strings of characters. The Morse code message reads: "segmentation of information is essence of coding." By analogy, segmentation or "chunking" of neuronal assemblies can be brought about by salient external stimulus sequences, brain-initiated, modality-specific synchronizing-blanking mechanisms (such as saccadic eye movement, sniffing,

whisking, active touch, licking, contraction of middle ear muscles, etc.), internally generated oscillations, or other syntactical mechanisms.

identified as an entity with segregated boundaries from its background (von der Malsburg, 1994). However, a paradox inherent in this strategy is that the "essential attributes" necessary for the identification of an object, thing, or idea are not universal properties of the external world but are created by the observing brain (Llinás, 2001; Buzsáki, 2006). Therefore, a fundamental question is how the cell assembly concept helps us to track down brain mechanisms of classification and categorization, exemplified by the often used antonym terms such as integration versus segregation, differentiation versus generalization, pattern separation versus pattern completion, or parsing versus grouping (Edelman, 1987; Tononi et al., 1994).

I suggest an alternative strategy to the representational approach of neuronal assembly identification. The main hypothesis is that the cell assembly concept is most useful from the point of view of downstream "observer-reader-classifier-integrator" mechanisms (referred to as "readers" hereafter) because the biological relevance of a particular constellation of active neurons (i.e., a presumed cell assembly or assembly sequence) can only be judged from the perspective of explicit outputs. An elementary classifier mechanism is the action potential of a reader neuron, which reflects the integration of the activity of an upstream assembly. The action potential is caused by the assembly activity. At the most complex level, such "caused" effects may be motor outputs, decisions, plans, recalls, and thoughts.

Sequences of unique assemblies (Figure 1A) evolve in both neuronal space and in time (Rabinovich et al., 2008a, 2008b). My second hypothesis is that, analogous to words and sentences in language, neuronal assemblies are organized by syntactical rules that define their first-order and higher-order relationships. Chunking information into smaller packages by syntactical rules, known to both sender and receiver, makes communication more straightforward than interpreting long uninterrupted messages (Figure 1B; Wickelgren, 1999). Furthermore, without syntactical rules that can silence assembly activity, an input would generate a perpetual reverberation of excitatory activity (Figure 1A; Lorente de Nó, 1938), potentially involving the entire brain.

If indeed cell assemblies and assembly sequences are parsed and separated in time, there must be mechanisms that bridge them across time even in the absence of spiking

whisking, active touch, licking, contraction of middle ear muscles, etc.), internally generated oscillations, or other syntactical mechanisms.

(C) Reader-defined cell assemblies. Neurons that fire within the time integrating window of a reader mechanism (e.g., the ability of a reader neuron to integrate its inputs within the time frame of its membrane time constant) define an assembly (irrespective of whether assembly members are connected synaptically or not). Readers a, b, c, and w may receive inputs from many neurons (1 to n) by way of synapses differing in strength but respond only to a combination of spiking neurons to which they are most strongly connected (e.g., reader a responds preferentially to cofiring of neurons 1, 5, and 9 at t_1 , even though it may be synaptically innervated by neurons 2, 6, and 10 as well; at t_2 , neuron b fires in response to the discharge of neurons 2, 6, and 10). Synaptic strengths between neurons vary as a function of the spiking history of both postsynaptic and presynaptic neuron (short-term plasticity). The response of the reader neuron, therefore, depends on both the identity of the spiking upstream neurons and the constellation of current synaptic weights ("synassemblies"). Reader mechanism q has a longer time integrator and, therefore, can link together assemblies to neural "words," reading out a new quality not present in the individual representations of a, b, and c.

activity (Buonomano and Maass, 2009). Therefore, the third hypothesis I advance is that the constituents of the neural syntax are linked together by dynamically changing constellations of synaptic weights (von der Malsburg, 1994), which I refer to as “synapsembles.”

Reader-Centric Definition of Cell Assembly

I suggest that an objective identification of the cell assembly requires two key conditions: a reader-classifier and a temporal frame. Neurons come together in transient time frames to produce a composite downstream effect, which cannot be achieved by single neurons alone. The most important modus operandi in this process is synchrony of events (Abeles, 1991; Engel et al., 2001; Fries et al., 2007; Hansel and Sompolinsky, 1992; Singer, 1999). In its broad definition, synchrony refers to the concurrence of events in time. However, this definition of synchrony is meaningful only from the perspective of a reader mechanism with the ability to integrate upstream events over time (Buzsáki, 2006). Thus, whether events are synchronous or not can be determined only by their impact on a reader-actuator. Similarly, I suggest that *the cell assembly can only be defined from the perspective of a reader mechanism.*

Even the simplest neural networks can give rise to multiple combinations of firing patterns (Abeles, 1991). Whether one or several of the possible combinations of firing patterns are meaningful can be determined only by a reader-classifier mechanism. If multiple combinations elicit the same output in one reader, they are interpreted as identical from the point of view of the reader. Another reader mechanism may respond to another set of combination of firing patterns. A simple and ubiquitous example of a reader mechanism in the brain is the integration of presynaptic spikes by neurons, constrained by their membrane time constant τ .⁴ A group of upstream neurons, whose spike discharges occur within the window of the membrane time constant of the reader-integrator neuron, and trigger an action potential, can be regarded as a meaningful neuronal assembly from the viewpoint of the reader neuron. Action potentials of other upstream neurons, which fire outside this critical time window (i.e., nonsynchronously), can only be part of another assembly. The reader-integrator mechanism can therefore objectively determine whether neurons are part of the same assembly and serve the same goal (i.e., the discharge of the reader neuron) or belong to different assemblies (Figure 1C). The length of τ is affected by a number of factors, including the background activity in the network and availability of subcortical neuromodulators (cf., Destexhe et al., 2003). In the intact waking cerebral cortex, τ of principal cells is approximately 10–30 ms (Koch et al., 1996).

Using the analogy of a musical assembly, in which the tempo of one member can be reasonably predicted from the activity of the other members of the orchestra, the spike occurrence of a neuron taking part in a cell assembly should be reliably predicted from the activity of its peer neurons. To illustrate such assembly cooperation, I draw an example from the hippocampus (for neocortex, see Truccolo et al., 2010).⁵ Spike timing of hippocampal pyramidal cells can be related to the position of the animal (O’Keefe and Nadel, 1978), to the phase of the local field potential (LFP) theta cycle (O’Keefe and Recce, 1993),

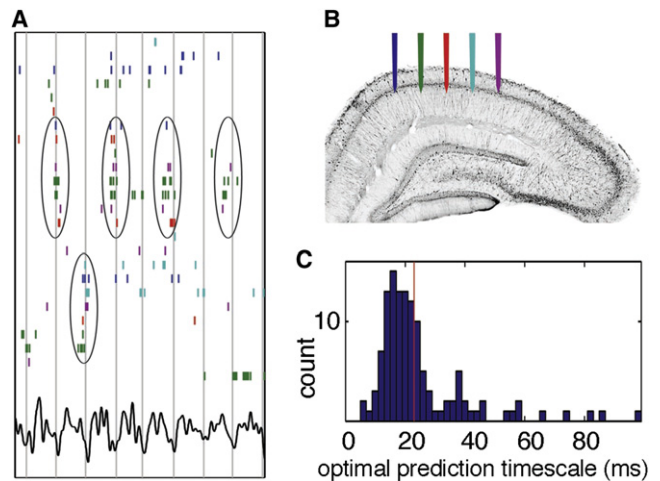


Figure 2. Cell Assembly: The Fundamental Unit of Neural Syntax

(A and B) Raster plot (A) of a subset of hippocampal pyramidal cells that were active during a 1 s period of spatial exploration on an open field out of a larger set of simultaneously recorded neurons, ordered by stochastic search over all possible orderings to highlight the temporal relationship between anatomically distributed neurons. Color-coded ticks (spikes) refer to recording locations shown in (B). Vertical lines indicate troughs of theta waves (bottom trace). “Cell assembly” organization is visible, with repeatedly synchronous firing of some subpopulations (circled). Note that assemblies can alternate (top and bottom sets) rapidly across theta cycles.

(C) Spike timing is predictable from peer activity. Distribution of timescales at which peer activity optimally improved spike time prediction of a given cell, shown for all cells. The median optimal timescale is 23 ms (red line). Modified with permission after Harris et al. (2003).

and to the spiking of other neurons. Each of these variables is correlated with the spiking activity of single neurons but with different temporal resolutions. Since spiking activity refers to events that occur in time, the best prediction of spike timing from the other variables should have an optimum time window. By varying the analysis window experimentally, the best prediction of the spike timing of single hippocampal neurons from the activity of other neurons was found when spiking of peer neurons was assessed in 10–30 ms epochs (Figure 2; Jensen and Lisman, 1996, 2000; Harris et al., 2003; Kelemen and Fenton, 2010; Lansner, 2009). When two cells with distinct place fields (O’Keefe and Nadel, 1978) were examined their activity was associated with the spiking of distinct peers and the formed assemblies could alternate in a fast sequence (Figure 2A). The participation of individual assembly members from trial-to-trial can vary much more than the whole assembly (Pouget et al., 2000). Given the similarity between the temporal window of the assembly lifetime and the time constant of pyramidal cells, *the postulated physiological goal of the cell assembly is to mobilize enough peer neurons so that their collective spiking activity can discharge a target (reader) neuron(s).* Because of anatomical constraints, various combinations of upstream cells, active in a short time window, converge onto different reader neurons in the target layer (Figure 1C). Whether different constellations of spiking upstream neurons are regarded as parts of the same assembly or rather as different assemblies is not inherent but requires the specification of the downstream classifier-reader neuron(s). Because of the all-or-none spike response of

the reader neuron, the reader-neuron-defined cell assembly denotes a discrete, collective unitary event, which I refer to as the *fundamental cell assembly* or assembly τ .

The physiological importance of the cell assembly's typical ephemeral lifetime is also supported by the fact that this time window temporally overlaps with the duration of AMPA receptor-mediated EPSPs and GABA_A receptor-mediated IPSPs (Johnston and Wu, 1995). Furthermore, the temporal interaction between these opposing postsynaptic effects largely determines the period of gamma frequency oscillations observable extracellularly as a local field potential (LFP; Atallah and Scanziani, 2009; Bartos et al., 2007; Bragin et al., 1995; Buzsáki et al., 1983; Csicsvari et al., 2003; Leung, 2004; Mann et al., 2005; Whittington et al., 2000). Finally, this timescale also corresponds to the temporal window of spike-timing-dependent plasticity (Magee and Johnston, 1997; Markram et al., 1997; cf., Bi and Poo, 2001). Given the temporal similarity of these basic physiological effects and their functional interactions, the integration time window of τ is therefore a critical reader mechanism that can define the content of gamma wave packet as the fundamental cell assembly. (Reader mechanisms with wider time integration windows can combine several assemblies; see below).

The reader-centric definition of the cell assembly differs from representation-based descriptions (Abeles, 1991; Braitenberg and Schuz, 1991; Gerstein et al., 1989; Hebb, 1949; Hopfield and Tank, 1986; Palm, 1982; Wickelgren, 1999) in some key aspects. Hebb's cell assembly is essentially a graph of synaptically interconnected excitatory neurons (Abeles, 1991; Hopfield and Tank, 1986; Palm, 1982, 1987; Wennekers et al., 2003). However, unless the active neurons produce an interpretable output, connectedness is not sufficient to define an assembly. For the reader-centric definition of the assembly, direct excitatory connections among assembly members are optional but not obligatory because what matters is that neurons of an upstream assembly fire within the integrating time window of the reader mechanism (Figure 1C). For example, in a prominent model of assembly sequences ("synfire chain"), what matters is that at least one neuron in the target layer responds to the inputs from the upstream layer, irrespective of whether neurons in the upstream layer are strongly connected or not (Abeles, 1991). Naturally, if the transiently formed assembly members are interconnected anatomically, their coactivation can strengthen their membership and facilitate their future joint recurrence.⁶ Therefore, while the reader-centric definition of a cell assembly incorporates key features of Hebb's definition, it also provides a functional meaning.⁷

I use the term "reader" as a metaphor to refer to a classifier-actuator mechanism. The reader is both an observer-integrator and a decision maker in the sense that it generates a tangible, measurable, and interpretable output. In the simplest case, the output is binary, such as an action potential of a neuron. The reader is not necessarily an independent, isolated unit, but it can be part of the assembly itself, much like members of an orchestra, where each member is a reader of others' actions. Separation of the reader mechanism from the assembly concept is needed only for a disciplined definition of neuronal alliances serving well-defined goals.

Neural Syntax: Rules that Integrate and Parse Fundamental Assemblies

In general, syntax (grammar) is a set of principles that govern the transformation and temporal progression of discrete elements (e.g., letters or musical notes) into ordered and hierarchical relations (e.g., words, phrases, sentences or chords, chord progression, and keys) that allow for a congruous interpretation of the meaning of language or music by the brain (Pulvermüller, 2010). In addition to language and music, grouping or chunking the fundamentals by syntax allows for the generation of a virtually infinite number of combinations from a finite number of lexical elements using a minimal number of rules in sign, body, artificial, and computer languages and mathematical logic (Port and Van Gelder, 1995; Wickelgren, 1999). Syntax is exploited in almost all systems where information is coded, transmitted, and decoded (Figure 1B). By analogy, I suggest that in the brain distinct time-integrating (reader) mechanisms define the syntax of cell assembly organization and form assembly sequences of various lengths, compiled from strings of the fundamentals (i.e., from τ assemblies).⁸ As in language, the meaning of various strings of assemblies (or neuronal "trajectories"; see below) depends on how the fundamentals are ordered and parsed (Pulvermüller, 2003). I suggest that neural syntax facilitates the formation of ordered hierarchies of trajectories from the fundamental cell assemblies (Figure 1C).

Using assembly τ as opposed to a single neuron as the fundamental unit of syntax has several advantages. Neuronal trajectories involving only a single or too few neurons at each step would be vulnerable, as a result of synaptic or spike transmission failures and neuronal damage. Assembly partnership tolerates spike rate variation of individual cells effectively since it is the intensity of assembly activity that matters for the reader. Furthermore, minor differences in synaptic weights between the leading neuron and followers would divert the trajectory in multiple directions in the presence of noise. In contrast, interacting assembly members can compute probabilities, rather than deterministic information, amplify inputs, and robustly tolerate noise even if the individual members respond probabilistically (Fiete et al., 2010; Geisler et al., 2007).

Neural Words and Sentences

The second hypothesis of this review is that temporal sequencing of discrete assemblies by neural syntax can generate neural words and sentences. Although strings of assemblies can be regarded simply as a larger assembly, and indeed assemblies of different length and size refer to many things in neuroscience, I chose the term "neural word" to emphasize that words consist of multiples of the fundamental assemblies. Gamma oscillation episodes, containing a string of assemblies, are typically short lasting (Engel et al., 2001; Fries, 2005; Gray and Singer, 1989; Whittington et al., 2000; Sirota et al., 2008) and often grouped by slower oscillations (Bragin et al., 1995; Canolty et al., 2006; Chrobak and Buzsáki, 1998; Hasenstaub et al., 2005; Sirota et al., 2008; Steriade, 2006). Such a relatively short sequence of cell assemblies may be regarded as a neural word (Jensen and Lisman, 1996, 2000; Lee and Wilson, 2002; Lisman, 1999; Skaggs et al., 1996).

Linking strings of fundamental assemblies requires readers with longer time integration abilities. In addition to the membrane time constant of single neurons, multiple other time integrators are present in the brain. NMDA receptors operate at the timescale of tens to hundreds of milliseconds (Monyer et al., 1992). Time integration of cell assemblies at the subsecond to seconds timescale can be performed by metabotropic glutamate receptors (Nakanishi, 1994), GABA_B receptors (Deisz and Prince, 1989), and slow afterhyperpolarization-associated conductances (Lancaster and Adams, 1986). Another time integration mechanism at this timescale, and at the level of a single neuron rather than a synapse, is the spiking-history dependence of spike threshold. After a burst or train of spikes but even after a single spike, the spike threshold increases measurably for tens to hundreds of milliseconds, independent of the synaptic inputs (Henze and Buzsáki, 2001; Mickus et al., 1999). Reader mechanisms of spiking activity at very long timescales may be exemplified, e.g., by the autonomic nervous system and the 0.1 Hz periodicity of the brain's "default networks" (Raichle et al., 2001).

Perhaps the most versatile class of reader-integrator mechanisms of neuronal assemblies is oscillations. Neuronal oscillators belong to the family of relaxation oscillators, with separable input (charging or receiving) and output (discharging, transmitting, or duty cycle) phases (Buzsáki, 2006; Pikovsky et al., 2001). This asymmetry is due mainly to the within-cycle offset of inhibition and excitation (Buzsáki et al., 1983; Csicsvari et al., 1999). The charging or accrual phase of the oscillator is a typical time integrator ("reader") mechanism of upstream activity. Oscillators are also natural parsing and chunking mechanisms of neuronal activity because they have well-defined onsets and offsets with characteristic maximum and minimum spiking activity of the information-transmitting principal cells (Masquelier et al., 2009). This stop-start parsing function of neuronal oscillators can determine the length of an information unit ("neural word" or assembly sequence), and multiple cycles can combine word sequences into "neural sentences." Since oscillator readers are a collective product of neuronal cooperation, their occurrence is reflected in the LFP. Therefore, along with other intermittent population events, such as K complexes, ponto-geniculo-occipital (PGO) spikes, and hippocampal sharp waves, LFP rhythms can be used conveniently as mesoscopic reader mechanisms by the experimenter. Assemblies active within a given classifier pattern, such as an oscillation cycle, can represent an integrated entity (e.g., a neural word).

A well-studied and understood example of a neural word is the spatiotemporal pattern of neuronal activity in the antennal lobe (AL) of insects in response to odor stimuli (Figures 3A–3C; Laurent, 2002; Laurent et al., 2001; MacLeod and Laurent, 1996). When an odor is presented, it induces a transient gamma frequency oscillation in the AL neuronal population, with different small subsets of AL neurons firing in each oscillation cycle. The odor is thus represented (or "coded") by an evolving sequence of activity vectors (a neural word or trajectory), lasting for a few hundred milliseconds. Successive presentations of the same stimuli evoke similar trajectories (Figure 3A, inset), whereas different odors are associated with uniquely different sequences

of projection neurons (Broome et al., 2006; Mazor and Laurent, 2005).

Another well-understood example of neural words is bird-songs. Birdsongs are induced internally rather than triggered by external stimuli. The song consists of distinct bursts of sounds (syllables), separated by silent intervals (Figure 3D).⁹ In the zebra finch, the syllable sequences are stereotypical and last for several seconds. The song is controlled by a set of nuclei, which form a mostly feed-forward excitatory pathway (Nottebohm et al., 1976). The critical brain area in song production is the high vocal center (HVC), which projects to the robust nucleus of the arcopallium (RA), which, in turn, drives the hypoglossal motor neurons innervating the vocal organ (syrinx). Experiments have demonstrated that the temporal structure of the song is generated by sparse sequential bursts of RA-projecting HVC neurons (Fee et al., 2004; Hahnloser et al., 2002; Long and Fee, 2008). Each neuron typically emits a single brief burst of spikes only at one time in the song (Figures 3D and 3E). It is assumed that each of the sequentially activated neurons is a part of an assembly of approximately 200 neurons, whose other members remain unseen to the experimenter (Hahnloser et al., 2002). The sequential activation of the assemblies in approximately 600 ms can be conceived as a word and the same word is repeated numerous times in a singing episode.¹⁰

When sequentially activated neural words are different, they can be conceptualized as a neural sentence. Numerous complex behavioral patterns, grouped under the term "fixed action patterns"¹¹ or "action syntax" (Lashley, 1951), can be elicited by a relevant cue or emerge without explicit cues. A well-studied fixed action pattern in rodents is grooming, a sequence of face washing followed by bilateral strokes, and the grooming sentence concludes with a postural turn and body licking. Although the neuronal mechanisms underlying the sequential patterns of grooming are largely unknown, the dorsolateral neostriatum may be involved in generating its syntax (Berridge and Whishaw, 1992).

Stereotypical actions can be generated by relatively simple feed-forward excitatory mechanisms (such as a "synfire" chain; Abeles, 1991; Hahnloser et al., 2002; Sompolinsky and Kanter, 1986;). However, generating multiple neuronal trajectories (i.e., neural sentence structures) serving different action sequences requires more sophisticated solutions. For example, nightingales or marsh warblers can sing dozens of unique songs. In this more complex case, the activation probability of a given assembly in the network probably depends not only on the immediately preceding but also on the previous sequence of a few (or several) assemblies. In strongly recurrently connected systems of large size, equipped with appropriate syntactical rules, very large numbers of trajectories (neural sentences) can be generated. In such model systems, the evolution of the assembly sequences (i.e., the uniquely different neural sentences) can be described by a transition rule where the future sequence is probabilistically defined by the previous ordering of assemblies (Jin, 2009; Rabinovich et al., 2008a, 2008b; Sakata and Brainard, 2006). Indeed, the ability of the brain to sweep through sequences of neuronal assemblies is expected to support our ability to reminisce, think, reason, and plan ahead.

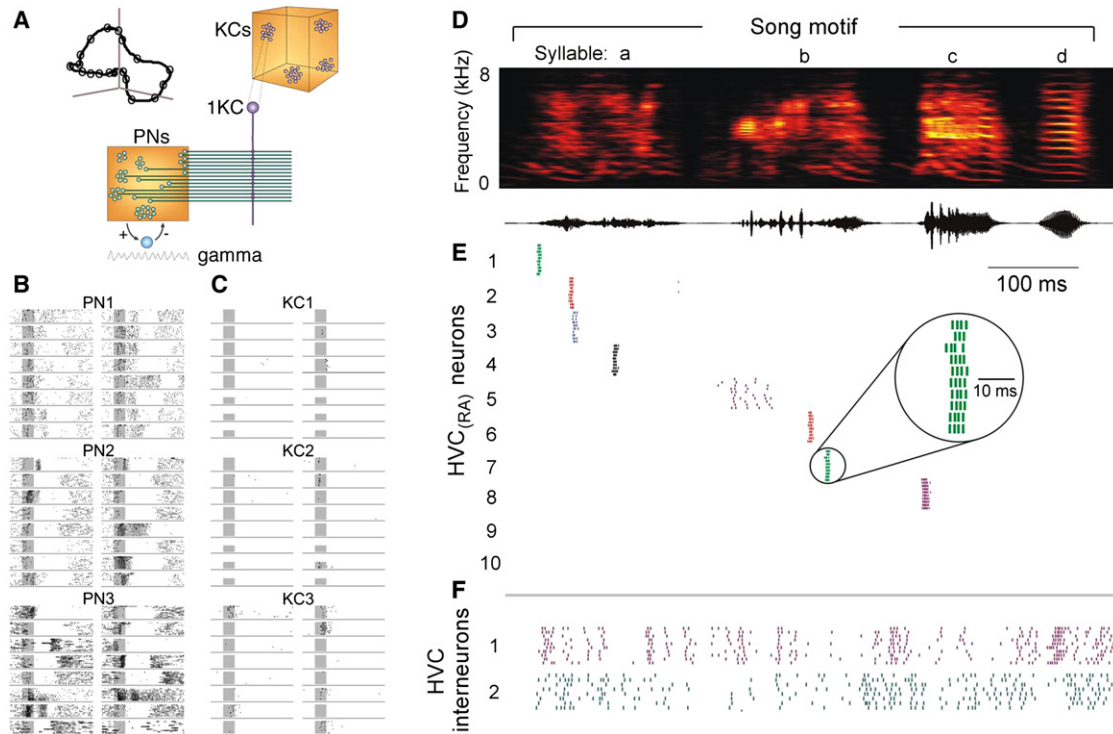


Figure 3. Externally Triggered and Internally Generated Assembly Sequences

(A) Wiring diagram of the early olfactory system of the locust. An odorant evokes an odor-specific temporal pattern in several of recurrently connected antennal lobe (AL) neurons, coordinated by a 20–30 Hz (gamma) oscillation. Kenyon cells (KC) of the mushroom body (MB) are the readers of the activity of AL projection neurons (PNs) and integrate their spikes.

(B) Firing patterns of 3 AL neurons (PN1–3) in response to 16 different odors. In each segment of time (e.g., a gamma oscillation cycle), a different constellation of AL neurons fires. This constellation is referred to as the “population vector” or “state” of the network, and the time-varying population vector (i.e., the shifting states) is described as a trajectory. Although each state of the trajectory codes for the same odor, the state evolves over a few hundred milliseconds before relaxing back to baseline activity (illustrated by the curve in the inset in A).

(C) Activity of 3 KCs. Each KC carries out a pattern matching operation between its connection vector and the PN population activity vector. The AL output synchrony is strongest at its early phase of evolution and evokes a single burst in the reader KC (“sparse coding”).

(D) Time-frequency spectrum of a zebra finch song and its amplitude envelope.

(E) Spike raster plot of eight projection neurons in the high vocal center (HVC). There is not a one-to-one correspondence between the song syntax and cell assemblies (neural “letters” in HVC). Rather, neurons in HVC generate a temporal “state” sequence (i.e., a trajectory), allowing the target neuronal activity and consequent motor actions unfold.

(F) Interneuronal activity is also temporally organized and relates to the syntactic structure of the song (F).

Panels (A) to (C) and panels (D) to (F) are modified with permission after [Laurent \(2002\)](#) and [Hahnloser et al. \(2002\)](#), respectively.

Large-scale recordings of neuronal spiking activity have recently been used to describe self-organized cell assembly sequences, serving mnemonic and planning functions, in the mammalian brain, as well as how they move the cognitive content forward or back in time ([Pastalkova et al., 2008](#)). Numerous experiments have demonstrated that hippocampal neurons show place-related firing while the rat explores or traverses its environment so that each assembly of hippocampal principal cells defines a particular position of space ([O’Keefe and Nadel, 1978](#); [Wilson and McNaughton, 1993](#)). It has been assumed that sequential activity of hippocampal “place cell assemblies” emerges in response to the changing constellation of environmental inputs ([O’Keefe and Burgess, 1996](#)) or to body-motion-derived cues ([McNaughton et al., 1996](#))—that is, that they are “driven” by sensory inputs. However, perpetually changing hippocampal assembly sequences could also be observed during the delay part of a memory task in the absence of changing sensory or feedback cues ([Figure 4A](#)). Importantly,

several measures of the place cell metric, including the duration of activity episodes of the neurons and the temporal relationship of their spikes relative to the reference theta oscillation cycle during translational behavior ([O’Keefe and Recce, 1993](#)), were similar in the internally organized sequences during the delay period, when the rats were required to run steadily in a wheel and remember a previously made choice ([Pastalkova et al., 2008](#)). The implication of these observations is that the physiological mechanisms that govern the progression of cell assembly sequences in the hippocampus during navigation and cognitive behaviors are quite similar. The behavioral relevance of self-organized sequential activity is emphasized by the observation that identical initial conditions (e.g., a left choice was rewarded) induced a similar assembly sequence each time, whereas different conditions (i.e., different memories) gave rise to uniquely different trajectories, which accurately predicted upcoming choices in the maze, including erroneous turns ([Figure 4A](#)). In situations when keeping track of two concurrent

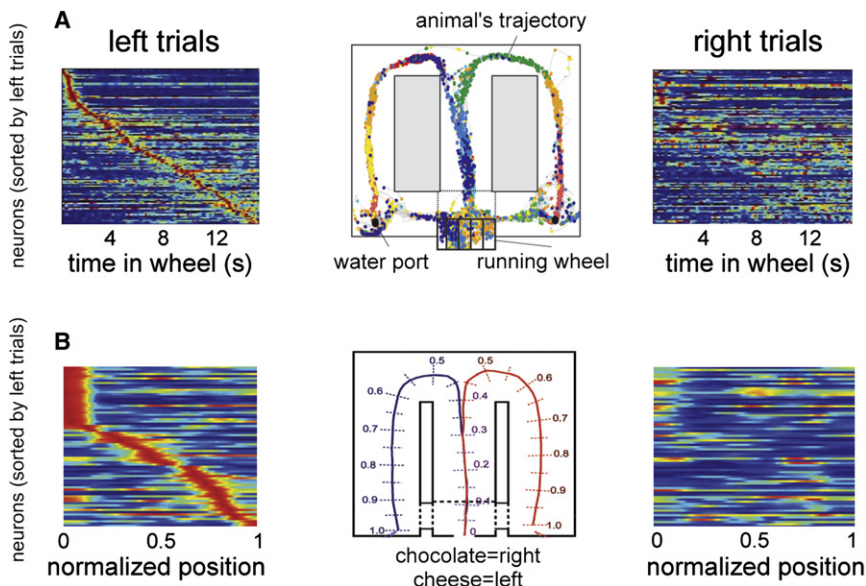


Figure 4. Internally Generated Assembly Sequences during Cognitive Activity

(A) Sequential firing patterns of hippocampal neurons in a memory task. Center: color-coded spikes (dots) of simultaneously recorded hippocampal CA1 pyramidal neurons. The rat was required to run in the wheel facing to the left during the delay between the runs in the maze. Left: normalized firing rate profiles of neurons during wheel running, ordered by the latency of their peak firing rates during left trials (each line is a single cell). Right: normalized firing rates of the same neurons during right trials.

(B) Sequential firing patterns of prefrontal pyramidal cells in a working memory task. Middle: cheese odor or chocolate odor in the start area signals the availability of cheese or chocolate reward in the left or right goal area (position 1), respectively. Travel trajectories were linearized (0 to 1). Left: neurons were ordered by the location of their peak firing rates relative to the rat's position in the maze during left trials. Each row represents the position-dependent normalized firing rate of a single neuron. Right: normalized firing rates of the same neurons during right trials.

Panels (A) and (B) are reprinted with permission from Pastalkova et al. (2008) and Fujisawa et al. (2008), respectively.

information streams (local and distant cues) were required for correct behavioral performance, two distinct assemblies toggled between representations of the two spatial frames (Johnson et al., 2009; Kelemen and Fenton, 2010). In accordance with experiments in rodents, single-unit studies in human patients showed that the hippocampus and entorhinal cortex can generate numerous trajectories corresponding to different memory episodes and, importantly, that the neurons that fire during free recall are part of the same cell assembly sequences that were activated while watching the cinematic episodes in the learning phase (Gelbard-Sagiv et al., 2008).

Generation of neural sentences is not confined to the hippocampal system. In the medial prefrontal cortex of the rat, neuronal sequences reliably differentiate between right and left trajectories in the maze prior to making a choice, with individual neurons active only for a short duration (Figure 4B; Baeg et al., 2003; Fujisawa et al., 2008). In summary, in contrast to the olfactory network and the birdsong system, cortical circuits can produce multitudes of unfolding assembly sequences in two different ways: either by responding to environmental/idiopathic stimuli, when such inputs are available, or by generating them internally.

Despite the robust correlation between assembly sequences and behavior, only limited evidence is available to support their critical importance in guiding overt behavior. Perhaps the best examples of the reader-centric definition of cell assembly sequences come from “brain-machine interface” (BMI) studies, where the reader-actuator mechanisms are explicitly defined. There are fundamentally two approaches to control cursors, robotic arms or other actuators by volitional control. In the first approach, large numbers of multiple units or LFP patterns from various cortical areas are recorded from and their assembly sequence activity is first correlated with a chosen natural behavior (e.g., arm movement). In this process, various statistical extraction methods are used to identify the conversion param-

eters that best describe the executed movement (Carmena et al., 2003; Chapin et al., 1999; Hochberg et al., 2006; Taylor et al., 2002). Spiking patterns of neurons that significantly contribute to the conversion parameters constitute the assembly sentence (Figure 5). In the next stage, these extracted parameters are used as a “transform algorithm” (i.e., a “statistical reader”) to control an actuator by brain activity. In the second approach, one or more neurons are chosen and their spiking activity is used to define the various degrees of freedom of the actuator (e.g., two neurons for 2D cursor). These effector neurons are then “trained” to generate the desired spike patterns needed to move the cursor. In this latter approach, it is left to upstream networks to “figure out” the successful, intention-controlled neuronal trajectories, without the need of an experimenter-designed complex transformation algorithm (Donoghue, 2002; Fetz, 1969, 2007; Kennedy and Bakay, 1998; Legenstein et al., 2010). The readers, in this case, are the effector neurons and their spiking activity defines the cell assembly sentences that lead to their patterned discharge. During the course of training, the natural proprioceptive feedback is substituted by visual observation of the movements of the effector device. By assigning a new goal, the relationship among the recorded neurons is modified and the muscular movements previously elicited by the firing patterns of the neurons can disappear (e.g., Fetz, 2007; Nicolelis and Lebedev, 2009), an explicit demonstration that different readers (muscles versus actuators) gain control over the coordinated assembly activity of neurons. The success of BMI experiments demonstrates that arbitrarily chosen reader-actuator mechanisms (goals) can rapidly reshuffle assembly members and neural sentences can be composed with remarkable ease.

Interleaved Cell Assembly Sequences Give Rise to Higher-Order Connections

Unlike in written language syntax, where contiguous series of fundamentals (letters) constitute words and sentences, in neural

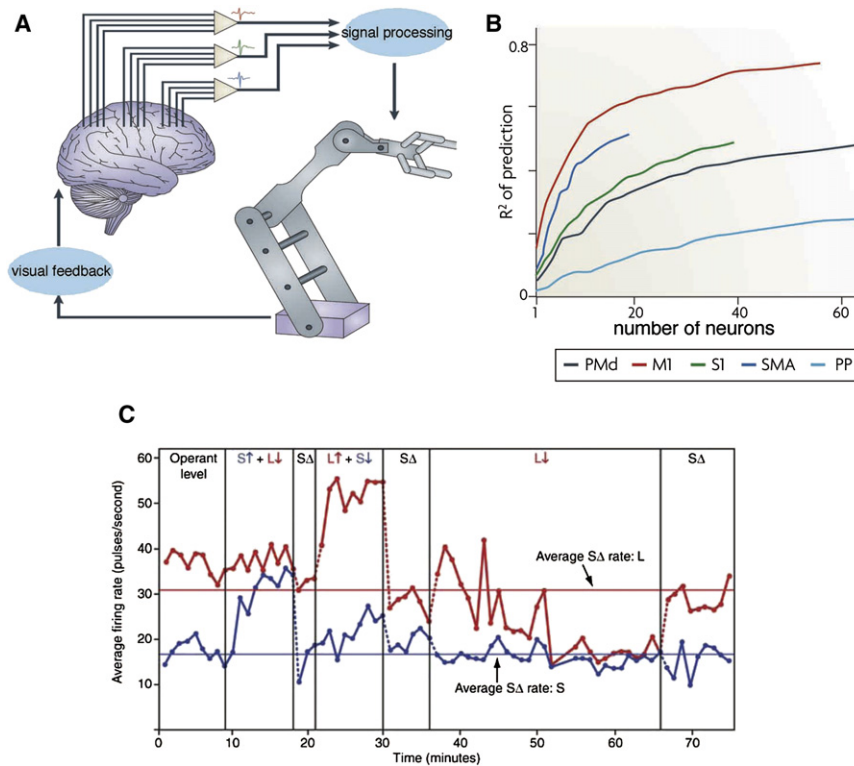


Figure 5. Schematic of a Brain-Machine Interface

(A) Schematic of a brain-machine interface (BMI). Activity from multiple ensembles of neurons in several brain areas is recorded and their movement-related information is extracted (“signal processing”). In the robot-control phase, the derived algorithm is used to convert ongoing neuronal activity to generate the desired movements of the robot (reader-actuator).

(B) Relationship between the numbers of neurons used to predict arm movement position in a monkey and accuracy of the algorithm’s prediction. Note that relatively few neurons are needed to achieve “good enough” performance, whereas very large numbers of neurons may be needed to achieve 100% accuracy. PMd, dorsal premotor cortex, M1, primary motor cortex, S1, primary somatosensory cortex, SMA, supplementary motor area and PP, parietal cortex.

(C) Differential control of neighboring neurons in the motor cortex by visual feedback in monkey. The firing rate of the one of the neurons (S, blue or L, red) controlled the displacement of a meter arm (Operant Level, upper row). Responses during epochs indicated by the red and blue arrows (upper row) were rewarded on the basis of an arbitrary increase or decrease of firing rate of the chosen reader neuron. The “reader” neurons (S or L) learned to respond differentially to the activity of (hidden) upstream assemblies within minutes.

Panels (A) and (B) and panel (C) are reprinted with permission from Nicolelis and Lebedev (2009) and Fetzi (2007), respectively.

syntax multiple words can overlap and generate both first-order and higher-order patterns, much like in music. Figure 6 illustrates the genesis and syntactic structure of such interleaved assemblies. The spiking patterns of hippocampal place cells can be approximated by a Gaussian spatial field, modulated by the theta frequency oscillation (Figures 6A and 6C; Samsonovich and McNaughton, 1997). The Gaussian fields of different place cells, representing upcoming places or items, can overlap and their temporal relationships are governed by a “compression” rule: within the theta cycle, the spike timing sequence of neurons predicts the upcoming sequence of locations in the path of the rat, with larger time lags representing proportionally larger distances (Figures 6A and 6C; Dragoi and Buzsáki, 2006; Skaggs et al., 1996).¹² The consequence of the time lags between the spikes of the transiently oscillating neurons is that the oscillation frequency of their *population output*, also reflected by the local LFP, is slower than the mean of the oscillating frequencies of the constituent neurons (Figures 6B and 6C, bottom part). The longer the theta timescale delays between the neurons, the slower the frequency of the population oscillation.

The tripartite relationship between global theta frequency f_{theta} , the oscillation frequency of single neurons f_o , and the distance-related, theta timescale temporal lags of spikes (time “compressed” sequences) has important consequences on the assembly organization of hippocampal neurons. First, the difference in oscillation frequency between the population (f_{theta}) and active single neurons generates an interference pattern, known as “phase precession” of place cells (O’Keefe and Recce, 1993), so that the distance traveled from the beginning

of the place field can be instantly inferred from the theta phase of the place cell spikes (Figure 6D; Dragoi and Buzsáki, 2006; Skaggs et al., 1996). Second, the slope of the phase precession defines the size of the place field (O’Keefe and Recce, 1993; Maurer et al., 2005). Neurons with identical place fields will fire at the same phase; thus, the observer neurons will classify them as members of the same assembly. Third, the field size (i.e., the “lifetime” of activity) is inversely related to the oscillation frequency of the neuron. As a result, neurons that oscillate faster have smaller place fields and display steeper phase-precession slopes, as is the case in the septal portion of the hippocampus, compared to neurons in more caudal (temporal) parts of the structure, which oscillate slower and have larger place fields and less steep phase-precession slopes (Kjelstrup et al., 2008; Maurer et al., 2005, 2006a; Royer et al., 2010a; Jung et al., 1994). The dynamic local adjustment of these interdependent parameters is responsible for the globally coherent theta oscillation in the hippocampal system (Bullock et al., 1990; Buzsáki, 2002; Geisler et al., 2010; Lubenov and Siapas, 2009).

Owing to the bidirectionally constrained relationship between single neurons and their population product, the time lags between spikes of neurons have important functional consequences. First, despite variable running speed of the rat, place cells continue to represent the same positions and distances in the same environment because the oscillation frequency of place cells increases in proportion with the velocity, while time lags remain essentially the same (Diba and Buzsáki, 2008; Geisler et al., 2007). Second, the duration of the theta cycle (120–150 ms in the rat) sets a natural upper limit of distance

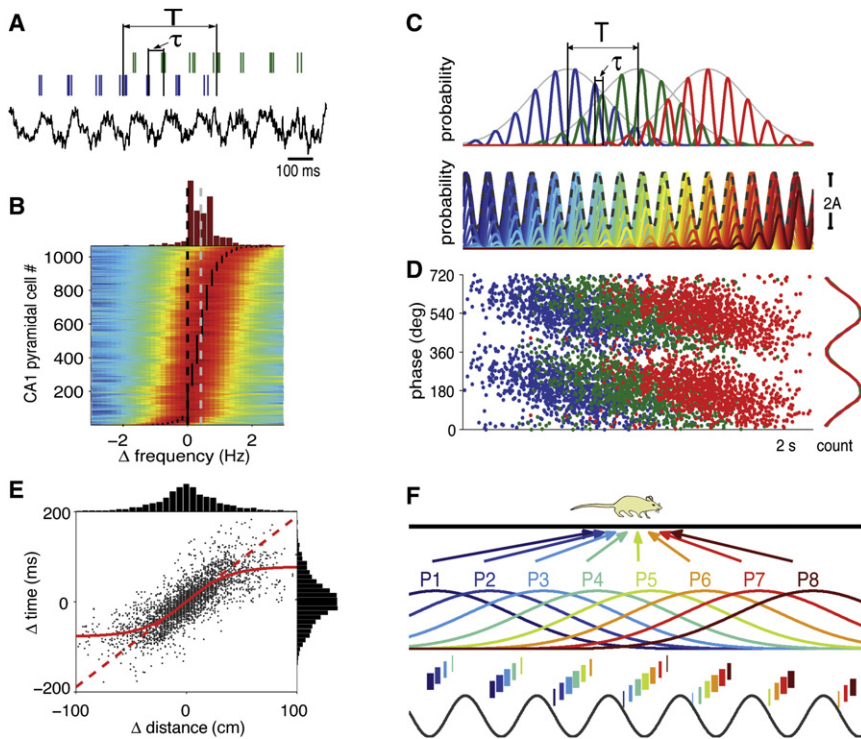


Figure 6. Interleaved Cell Assemblies

(A) Spiking activity of two hippocampal neurons (blue and green ticks) and LFP theta in a single run (1 s is shown). Temporal distance T is the time needed for the rat to run the distance between the peaks of the two place fields (“real time”). τ , time offset between the two neurons within the theta cycle (“theta time”).

(B) Distribution of oscillation frequencies of CA1 pyramidal cells ($n > 1000$) during running on the maze relative to the reference LFP theta (8.09 Hz = 0 Hz). Gray dashed line: mean oscillation frequency of pyramidal cells (8.61 Hz = 0.52 Hz). Note that nearly all place cells oscillate faster than the frequency of the concurrent LFP theta.

(C) Three example model neurons (color-coded) with identical oscillation frequency but different phase onset, according to their maximal discharge location. Bottom: the summed activity of the entire population of model neurons (black dashed line) oscillates slower than each transiently active individual neuron (color-coded).

(D) The phase of the three example neurons with respect to the oscillation of the population is plotted against time. Note that the neuronal spikes phase-precess approximately 360° (O’Keefe and Recce, 1993). Right: spike density for the example neurons.

(E) Correlation between the distances of place fields peaks and theta-scale time lag for > 3000 pairs of neurons (as in A). Above and right: histograms of distance and time lag, respectively.

(F) Interleaved neuron sequences represent position and distance relationships. The width of the

bars indicates firing intensity of the hypothesized assemblies while the theta timescale temporal differences between assemblies reflect their respective distance representations. In successive theta cycles, assemblies representing overlapping place fields (P1 to P8) shift together in time and sustain a temporal order relationship with each other so that the assembly that fires on the earliest phase represents a place field whose center the animal traverses first. The temporal compression mechanism (Skaggs et al., 1996) allows distances to be translated into time. Approximately 7 ± 2 assemblies/gamma cycles, are present in a given theta period (Bragin et al., 1995; Lisman and Idiart, 1995). The assembly sequences within theta cycles could be conceived as a neural word. Note that neighboring overlapping words differ only by one assembly. The rat has to travel 7 ± 2 theta cycles until a word with entirely different assemblies appear. Panels (A) to (E) and panel (F) are modified with permission after Geisler et al. (2010) and Dragoi and Buzsáki (2006), respectively.

coding by theta timescale lags (~ 50 cm for neurons in the dorsal hippocampus; Dragoi and Buzsáki, 2006; Maurer et al., 2005), as reflected by the sigmoid relationship between the theta time lags of neuronal spikes and distance representations (Figure 6E; Diba and Buzsáki, 2008). The behavioral consequence of the sigmoid relationship is that objects and locations > 50 cm ahead of the rat are initially less distinguishable from more distant landmarks, but as the animal approaches, they are progressively better resolved by the interleaved cell assemblies. Third, the number of cell assemblies that can nest in a given theta period (seven to nine, as reflected by the number of gamma cycles/theta; Bragin et al., 1995; Buzsáki et al., 2003; Chrobak and Buzsáki, 1998), determines the spatial resolution distance representation (approximately 5 cm/theta cycle). A consequence of the limited number of theta-nested assemblies is that distance resolution scales with the size of the environment; temporal lags that represent fine spatial resolution in small enclosures correspond to coarser distance representations in larger environments (Diba and Buzsáki, 2008; Fenton et al., 2008; O’Keefe and Burgess, 1996).¹³

Assuming that locations can be regarded analogous to discrete items (Figure 6F; Dragoi and Buzsáki, 2006; Lisman and Idiart, 1995), the temporal compression mechanism can limit the “attention span” and the “register capacity” of the memory “buffer” of the gamma-nested theta-cycle to seven to nine items

(Lisman, 1999; Lisman and Idiart, 1995; Jensen and Lisman, 1996; Hasselmo et al., 2002).¹⁴ In this latter context, the sigmoid relationship suggests that the spatiotemporal resolution of an episodic recall is high for the conditions/context that surround a recalled event, whereas the relationships among items representing the far past or far future, relative to the recalled event, are progressively less resolved (Diba and Buzsáki, 2008). However, as the content of the recall moves forward in perceived time, subsequent events gain high contextual resolution (Dragoi and Buzsáki, 2006). The theta dynamic-controlled delays imply that the speed of recall is generic and independent of the temporal relations of the items presented during encoding.

In strongly recurrent systems, such as the hippocampal CA3 region, the temporal compression mechanism (Skaggs et al., 1996) can ensure that in a neural word not only adjacent assemblies but also next-neighbor and more distant assemblies can be linked, as long as they consistently co-occur in the same theta cycles. These higher-order connections, in turn, can provide a substrate for alternative routes in the evolution of neuronal trajectories; for combination of different assembly sequences, mechanisms necessary, e.g., for solving detour and transitive inference problems (Dusek and Eichenbaum, 1997; Muller et al., 1996); and for higher-order associations in episodic memory (Polyn and Kahana, 2008). Thus, if the recall of a learned chain of fundamental assemblies a, b, c, and d is blocked at c,

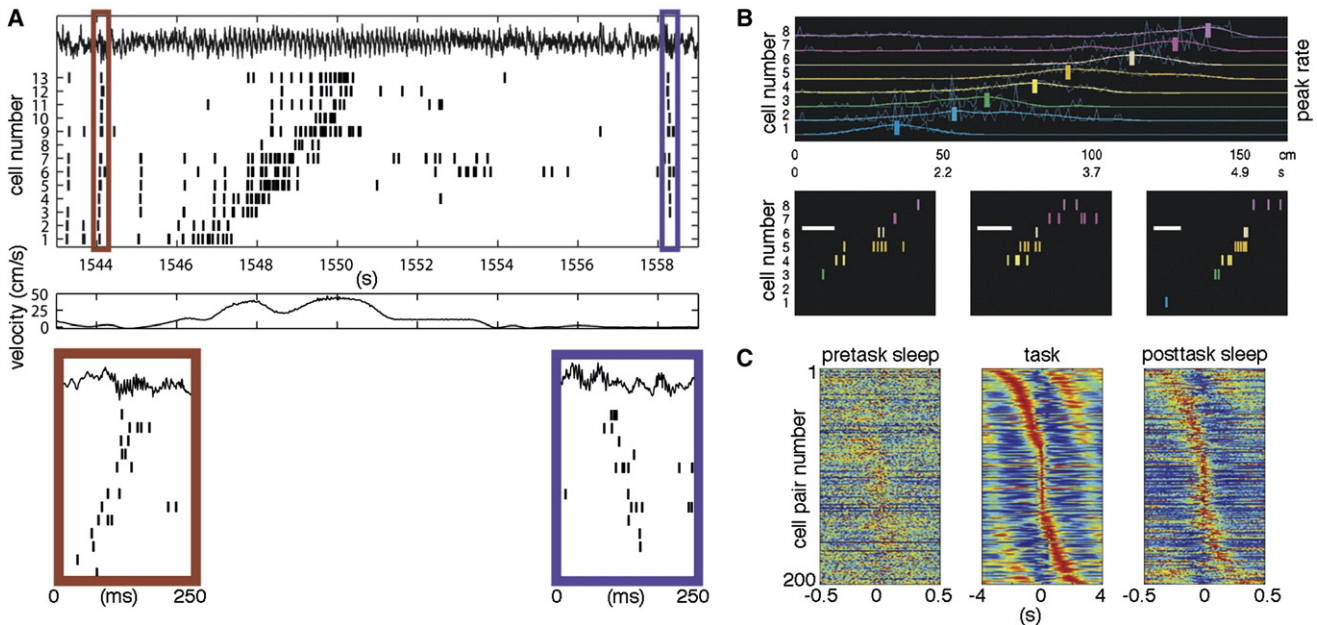


Figure 7. “Offline” Replay of Learned Neural Patterns

(A) Forward and reverse preplay and replay of place-cell sequences.

(A) Spike trains of 13 neurons during a single lap (CA1 local field potential shown on top). Bottom panels magnify 250 ms sections of the spike train, depicting forward preplay and reverse replay, respectively. Each place cell is assumed to be a member of an assembly of distributed hippocampal neurons defining a particular position, and the ensemble sequence constitutes a neural word.

(B) Replay of waking neural words during sleep in hippocampus. Smoothed place fields (colored lines) of 8 place cells during runs from left to right on a track (average of 30 trials). Vertical bars mark the positions of the normalized peaks of the smoothed fields. Nonuniform time axis below shows time within an average lap when above positions were passed. Bottom panels: three SPW-R-related sequences from slow-wave sleep after the waking session. Note similar sequences during SPW-Rs and run. Note also difference in timescale. The scale bar represents 50 ms.

(C) Time-compressed replay of waking assembly sequences during sleep in mPFC. Sorted cross-correlations from simultaneously recorded cell pairs. Each row in each subpanel shows the cross-correlation between a single pair of cells, sorted according to the temporal offset of the maximum peak during the task. Red indicates the highest coincidence rate and blue the lowest. The time axis during sleep epochs is magnified. Note similar sequences during the task and posttask sleep.

Panels (A), (B), and (C) are modified with permission after Diba and Buzsáki (2007), Lee and Wilson (2002), and Euston et al. (2007), respectively.

the trajectory may jump to assembly d, i.e., to the second-order partner of assembly b (Kistler and Gerstner, 2002; Kiebel et al., 2009; Rabinovich et al., 2008a).

Since a similar temporal dynamic is at play in the entorhinal cortex (Burgess et al., 2007; Chrobak and Buzsáki, 1998; Hasselmo et al., 2009; Mizuseki et al., 2009; Moser et al., 2008), prefrontal cortex, and other structures (Benchenane et al., 2010; Berke et al., 2004; DeCoteau et al., 2007; Jones and Wilson, 2005; Siapas et al., 2005; Sirota et al., 2008; Tort et al., 2008), the mechanisms explored in the hippocampus may apply to these structures as well.

Offline Replay of Assembly Sequences

While the time lags between assemblies in the hippocampus depend on theta-nested gamma waves during exploration, assembly sequences can occur both in the absence of theta (or other oscillations and environmental inputs). During consummatory behaviors, immobility, and non-REM sleep, the hippocampal theta rhythm is replaced by irregular sharp waves (Buzsáki et al., 1983). Self-organized population bursts of the hippocampal CA3 pyramidal cells induce a strong depolarization in the apical dendrites of CA1 pyramidal cells, reflected by an LFP sharp wave of negative polarity, accompanied by a transient fast-field

oscillation (140–200 Hz) or “ripple” confined to the cell body layer of CA1 pyramidal cells (Buzsáki et al., 1992; O’Keefe and Nadel, 1978). SPW-Rs are the most synchronous assembly pattern in the mammalian brain (Chrobak and Buzsáki, 1994), characterized by a 3- to 5-fold gain of network excitability (Csicsvari et al., 1999). SPW-Rs have been hypothesized to play a critical role in transferring transient memories from the hippocampus to the neocortex for permanent storage (Buzsáki, 1989; McClelland et al., 1995). In line with this postulated role, both place cell sequences and the distances between the place fields experienced during exploration are reflected in the temporal structure of neuronal sequences during SPW-Rs (Figures 7A and 7B; Kudrimoti et al., 1999; Lee and Wilson, 2002; Nádasdy et al., 1999; O’Neill et al., 2008; Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994) and their selective elimination after learning interferes with memory consolidation (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009). In the waking animal, SPW-R-related sequences can be replayed in either a forward manner, typically prior to initiating a journey, or in a reverse order after reaching the goal (Figure 7A; Diba and Buzsáki, 2007; Foster and Wilson, 2006). This bidirectional reenactment of temporal sequences may also contribute to the establishment of higher-order associations in episodic memory.

Offline replay of waking experience-dependent activity has been also observed in the neocortex (Figure 7C; Euston et al., 2007; Hoffman and McNaughton, 2002; Huber et al., 2004; Johnson et al., 2010; Takehara-Nishiuchi and McNaughton, 2008) and striatum (Lansink et al., 2008; Pennartz et al., 2004), as well as across structures (Ji and Wilson, 2007; Lansink et al., 2009), illustrating that it is a general phenomenon in the brain. Sleep-related assembly sequences are perhaps the strongest evidence for the occurrence of complex self-organized patterns in the brain independent from the influence of the environment. However, in contrast to the internally generated neuronal sentences underlying cognitive operations, such as recall, imagination, decision making, or action planning, which occur in real (clock) time, assembly replay during rest and sleep occurs in snippets and is faster, often compressed by at least a factor of ten compared to the behavioral timescale of neuronal activation (Davidson et al., 2009; Diba and Buzsáki, 2007; Euston et al., 2007; Foster and Wilson, 2006; Nádasdy et al., 1999). Although this time compression is only slightly faster than that generated by the theta-scale compression of distances, the main difference is that in contrast to the waking brain, there are no concurrent real time assembly sequences present during slow-wave sleep. Thus, while neuronal processing is perpetual in all brain states, conscious experience of such processing may require real time neural words and sentences.¹⁵

Since there are no immediate behavioral consequences of the “offline” state-related cell assembly sequences, one can only assume that the utility of such self-organized patterns is to strengthen or consolidate the synaptic changes initiated during the waking experience and to link assembly representations, which never or rarely overlapped during behavior. The responding reader-integrator neurons of such novel replay patterns will be different from the readers representing each experience separately. As a result, such offline linking of experiences may facilitate their associations in future waking states.¹⁶

Synapsembles Link Spiking Cell Assemblies

According to Hebb’s definition (Hebb, 1949), an assembly is characterized by the stronger synaptic connectivity among assembly members than with other neurons. In principle, chains of slow firing neurons, connected with predetermined and fixed synaptic weights, can form groups and propagate activity (Abeles, 1991). However, strong, “fixed” connectivity may not be a good model for segregating neuronal groups since synaptic weight distributions are perpetually changing in an activity-dependent fashion in the working brain. In fact, the dynamic range of short-term synaptic plasticity is large and similar to that of long-term plasticity (Marder and Buonomano, 2003), posing problems for the synaptic connection-based definition of cell assemblies. It follows that knowledge of spiking activity is insufficient to properly describe the state of the cortical network unless the distribution of momentary synaptic weights, i.e., the instantaneous functional connection matrix, is also known.

While spikes are generally regarded as the common currency of neuronal communication, experimental and theoretical studies over the past decade have accumulated compelling evidence that short-term synaptic plasticity can also serve

related functions (Abbott and Regehr, 2004; Abbott et al., 1997; Maass and Markram, 2002; Mongillo et al., 2008; Sussillo et al., 2007; von der Malsburg, 1994; Zucker and Regehr, 2002). Connectivity in the cortex is characterized by a large range of variation of synaptic weights (Gloveli et al., 1997; Holmgren et al., 2003; Markram et al., 1998; Reyes et al., 1998; Wang et al., 2006), which can change dynamically by both presynaptic and postsynaptic mechanisms (Chung et al., 2002; Deisz and Prince, 1989; Gupta et al., 2000; Markram et al., 1998; Thomson et al., 2002). The fraction of potentiating and depressing synapses is approximately the same in the intact neocortex (Fujisawa et al., 2008; Markram et al., 1998). Indeed, a balance between depressing and potentiating synapses in model networks is needed for stability. At the same time, networks with dynamic synapses can respond robustly to external inputs yet return to baseline activity shortly after the perturbation (Sussillo et al., 2007). Analogous to the assembly of spiking neurons, a particular constellation of synaptic weights in a defined time window can be conceived of as an assembly of synapses or “synapsemble.” There are orders of more synapses in the brain than the number of its neurons. In addition, dynamic synapses signal a continuous relationship between neurons, offering a much richer source of communication by synapsembles than by the all-or-none spikes or discharge rates.

Despite the expected critical role of synapsembles in neural syntax, experimental evidence supporting the role of synapsembles in combining and separating neuronal assemblies is scarce, largely because of the lack of tools to directly measure synaptic connectivity in the behaving animal. An indirect measure of short-term plasticity can be obtained by examining the fine-time-scale spike transmission probabilities between simultaneously recorded neurons (Baeg et al., 2007; Constantinidis and Goldman-Rakic, 2002; Fujisawa et al., 2008; Hirabayashi and Miyashita, 2005). Even with this indirect method, only connections between principal cells and interneurons can be studied reliably with current methods (Figure 8A). As Figure 8 illustrates, synaptic efficacy (defined operationally as the magnitude of excess coincidental spikes at < 3 ms latencies between the pre- and post-synaptic neuron; Fujisawa et al., 2008) between connected pairs is not constant but varies both as a function of the animal’s position in the maze (Figure 8B) and as a function of left versus right trajectories (Figure 8C). Remarkably, the temporal span of the effective spike transmission between pyramidal cell-interneuron pairs is comparable to the activity lifetime of the principal cells in both hippocampus and prefrontal cortex (Figure 4), implying that synaptic plasticity may play a role in limiting the duration of cell assemblies by controlling their temporal and spatial evolution.

I hypothesize that synapsembles may serve a dual role. First, they limit the lifetime of neural words to subsecond to seconds timescales. Such self-tuned synapses are probably critical in the build up and termination of assembly activity. This process may be brought about by the depressing excitatory synapses among the active assembly members and/or by potentiated inhibition of the recruited interneurons, assisted by intrinsic neuronal mechanisms, such as firing-history dependence of spike threshold (Henze and Buzsáki, 2001). Second, synapsembles link neuronal words separated by cessation of spiking activity (Buonomano and Maass, 2009). Depressing the

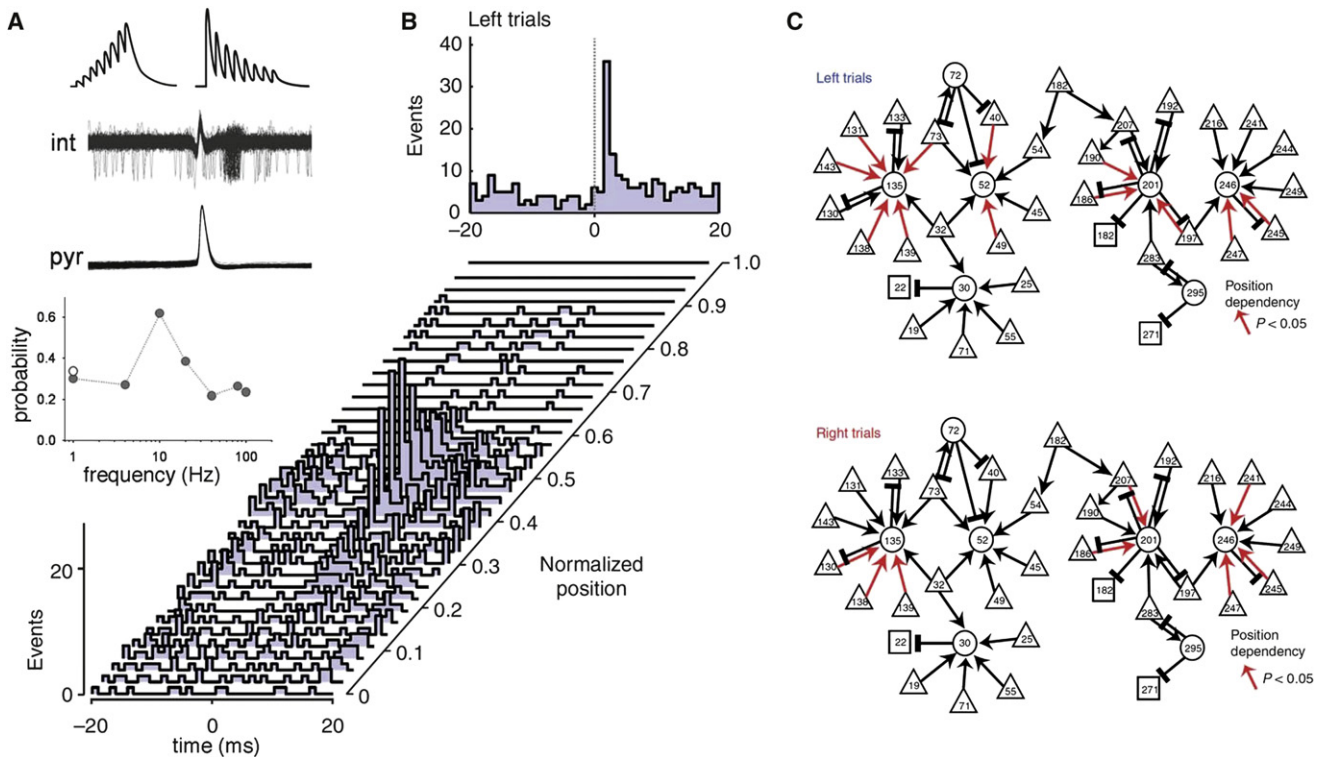


Figure 8. Short-Term Synaptic Plasticity in a Working Memory Task

(A) Top: illustration of facilitating and depressing synaptic connections between pyramidal cell and interneuron, as reflected by the changes of EPSPs in the post-synaptic neuron. Middle: superimposed traces (10 ms) of intracellular recording from a hippocampal CA1 pyramidal cell (pyr) and extracellular recording from a putative interneuron (int), aligned by the intracellular action potential. Note short-latency (<2 ms) discharge of the interneuron after the spike of the presynaptic pyramidal cell (visible also as an artifact on the extracellular trace). Bottom: dependence of spike transmission probability on the frequency of the presynaptic pyramidal cell spikes. Note that the highest spike transmission probability occurs at approximately 10 Hz.

(B) Short-term cross-correlograms between a putative pyramidal cell-interneuron pair in the prefrontal cortex as a function of the rat's position during left-turn trajectories. The most effective transmission occurred near the choice point (positions 0.3–0.5). Top right: session mean.

(C) Task-dependent changes of synaptic strengths (red arrows) between putative pyramidal cells (triangles) and interneurons (circles) in a small prefrontal network.

Panel (A) and panels (B) and (C) are reprinted with permission from Marshall et al. (2002) and Fujisawa et al. (2008), respectively.

inhibitory connections and/or potentiating excitatory synapses between members of the receding and trailing cell assemblies (Wang et al., 2006) may achieve such linking. Clearly, the postulated contribution of self-tuned synaptic plasticity to neural syntax could benefit from future experimental and computational analyses.

Segregation of Cell Assemblies by Inhibition

Segregation of excitatory principal cells into functional groups is made possible by inhibition, and this grouping-parsing function is perhaps the most fundamental task performed by the large family of interneuronal classes in the cortex (Freund and Buzsáki, 1996; Klausberger and Somogyi, 2008). As an illustration, consider a ring of excitatory neurons with just one inhibitory interneuron in the middle, reciprocally connected to the excitatory cells (Figure 9A). An external input to any of the neurons may activate a subset of the ring neurons while silencing others. The interneuron-guided grouping (i.e., formation of a candidate assembly) depends on the location of the input in the ring and, critically, on the fine details of synaptic strengths (i.e., the structure of the synapse). With different initial conditions,

the interneuron can be “enslaved” to different constellations of excitatory neurons. This example also shows that there is a temporally exquisite relationship between the active assembly, the interneurons, and the silenced population. The assembly forming/segregating ability of interneurons may be due to the efficient synapses formed between pyramidal cells and interneurons (Csicsvari et al., 1998; Galarreta and Hestrin, 2001; Geiger et al., 1997; Gulyás et al., 1993; Maurer et al., 2006b; Miles, 1990; Thomson et al., 2002) and strong inhibitory interneuron-pyramidal cell connections (Cobb et al., 1995; Pouille and Scanziani, 2001), relative to the typically weak synapses linking principal cells (Miles, 1990).

In the neocortex, inhibition can have either a positive or inverse correlation with excitatory thalamic input (Ferster, 1986; Gentet et al., 2010; Wehr and Zador, 2003;). Excitatory and inhibitory inputs interact in a complex manner to shape the response to On and Off transitions of the stimulus (Borg-Graham et al., 1998) or to affect the tuning properties of the principal cells (Monier et al., 2003; Wilent and Contreras, 2005). Similarly, the firing rates of interneurons in the hippocampus often vary as a function of the animal's position (Figure 9B; McNaughton

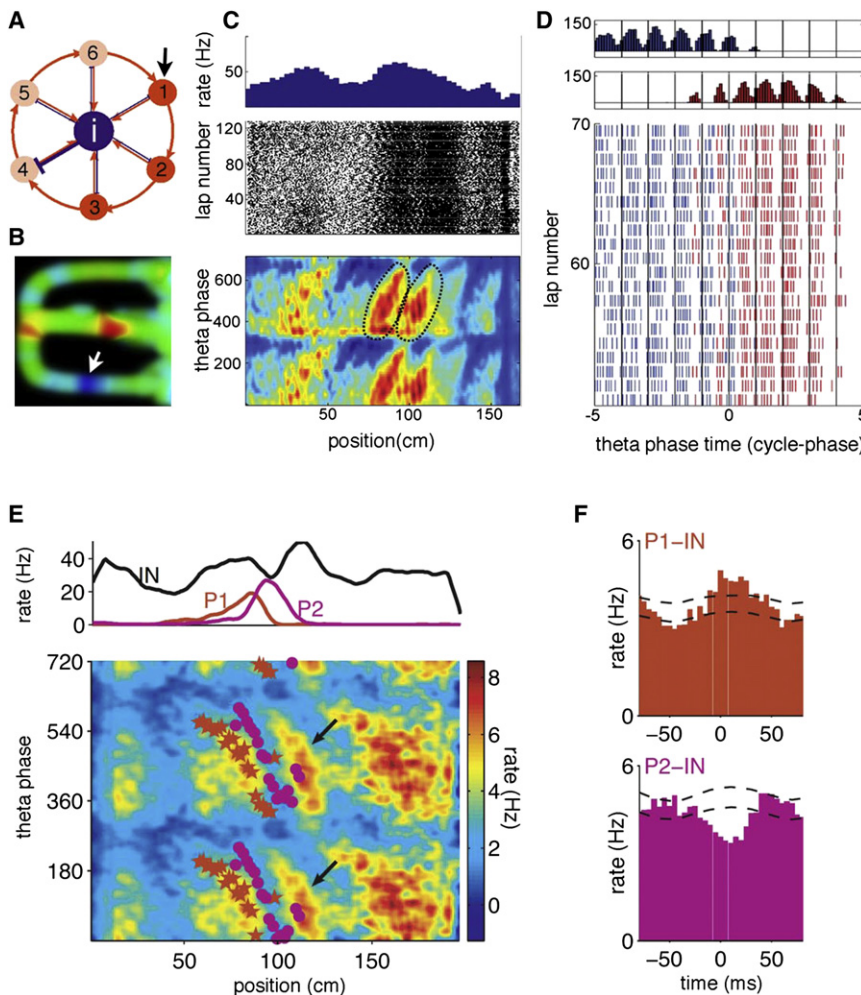


Figure 9. Segregation of Cell Assemblies by Inhibition

(A) A ring of pyramidal neurons (1–6), mutually innervating an interneuron (i). The synaptic strength between the interneuron and pyramidal cell 4 is stronger than between other pairs. When pyramidal cell one receives an input (arrow), cells 1 to 3 are activated while 4 to 6 remain silent (segregated).

(B) CA1 hippocampal interneuron carrying spatial information. Firing rate map of the neuron in a figure-eight-shaped maze. Red, 56 Hz, dark blue, ~0 Hz. Note silent “place field” (arrow) in the lower arm.

(C) An interneuron can belong to two assemblies within the same theta cycle. Firing rate, spikes in each lap, and theta phase of spikes of the interneuron as a function of position. Phase distributions are shown twice for better visibility. Place field boundaries were assigned according to the phase precession of the interneuron (black ellipsoids).

(D) Event-triggered average of spike times (top), aligned on the time of the theta peak that occurred nearest (in time) to the point of maximum spatial overlap of the two fields (blue, first field encountered; red, second field encountered). Time is in units of phase relative to the trigger point in the middle of the field. Bottom: spikes of the interneurons in successive laps. Note that the systematic phase precession of spikes uncovers two independent but overlapping fields (blue and red spikes), an indication that the interneuron can switch assembly partnerships even within the same theta cycle.

(E) Firing rates of two pyramidal cells (red, P1; magenta, P2) and a putative basket cell (black, IN) as a function of position (top). Bottom: mean phase precession of P1 (stars) and P2 (dots), superimposed interneuron’s color-coded smoothed density of firing. Note the similar phase slope of P1 and the interneuron.

(F) Temporal cross-correlation between P1 and interneuron IN and P2 and the interneuron shown in (E). Note positive temporal correlation between P1 and IN and negative correlation between P2 and IN. The dashed lines indicate the 95% confidence interval for shuffled spike trains.

between P1 and IN and negative correlation between P2 and IN. The dashed lines indicate the 95% confidence interval for shuffled spike trains. Panel (B) is courtesy of K. Mizuseki. Panels (C) and (D) and panels (E) and (F) are reprinted with permission from Maurer et al. (2006b) and Geisler et al. (2007), respectively.

et al., 1983) and can mimic several signatures of place cells, including positional information, field size, speed modulation of rate and oscillation frequency, and phase precession (Ego-Stengel and Wilson, 2007; Marshall et al., 2002; Maurer et al., 2006b; Geisler et al., 2007; Wilent and Nitz, 2007). Importantly, the input-related specific patterns are not only associated with increased but also with selectively decreased firing of inhibitory interneurons in both neocortex and hippocampus (Figure 9B; Gentet et al., 2010; Rao et al., 1999; Wiebe and Staubli, 2001; Wilent and Nitz, 2007). Such well-defined suppression of inhibitory neurons in a neural sentence may facilitate the emergence of new assemblies, suppressed by the same interneurons in other parts of the sentence. How can inhibitory neurons play such a two-faced role: to be part of an assembly and also suppress competing assemblies? Since assembly members are typically drawn from sparsely firing neurons of a large neuron network (Fujisawa et al., 2008; Harris et al., 2003; Sakata and Harris, 2009), only a few principal cells are typically active in a given volume of tissue at any given time. Although interneurons are

expected to respond to all of their principal cell inputs more or less equally, in a given short time window only one or a few strongly active principal cells discharge them, thereby essentially “copying” the principal cell’s firing pattern. In turn, the transiently active interneuron can suppress the activity of competing principal cells in the vicinity of their (mostly local) axon collaterals. As a result, only a single assembly (the “winner”) may be active at a time even in a large neuronal volume.

An example of the firing-pattern-mimicking behavior of hippocampal interneurons is the theta phase precession of their spikes. In contrast to pyramidal cells, the spikes of hippocampal interneurons are either locked to a narrow phase of the theta cycle or show broad phase distribution with dominant locking to the trough. However, whenever an interneuron spike displays a transient phase shift, its phase precession slope is similar to that of the pyramidal cell(s) to which the interneuron is monosynaptically connected (Maurer et al., 2006b). Because multiple interleaving place cell assemblies are present in a given theta cycle (Figure 6), it is expected that the active assemblies induce

selective firing in their own interneuron targets at discrete theta phases. This is indeed the case (Figures 9C and 9D). While the firing rate of the example interneuron in Figure 9C gives little indication that it is driven by neurons taking part in two assemblies, two separate phase precession cycles are clearly revealed in “phase-space” (arrows in Figure 9C). Using the spike phase information, two distinct place-related firing patterns of the same interneuron can be readily segregated, each with a monotonic phase dynamic (Figure 9C), an indication that its firing is under the control of two distinct cell assemblies. In addition, Figure 9D shows that some interneurons not only are driven specifically by assemblies but also actively contribute to the segregation of competing assemblies. In this example, two spatially overlapping place cells were simultaneously recorded with a putative basket interneuron (Geisler et al., 2007). The gamma timescale positive correlation between one place cell (P1) and the interneuron suggests that both cells belonged to the same cell assembly. In contrast, the spiking activity and phase precession of the second place cell (P2) was anticorrelated with the discharge of the interneuron (Figure 9D), indicating an enabling mechanism of the interneuron at times when P2 and its assembly peers were active.

In summary, the available research points to the critical roles of interneurons and inhibition in the formation and segregation of cell assemblies, and in organizing their temporal evolution (c.f., Rabinovich et al., 2006). Given the diverse interneuron classes in the cortex (Freund and Buzsáki, 1996; Klausberger and Somogyi, 2008; Markram et al., 1998), it is expected that further research will identify novel mechanisms by which the different classes interact with each other and the principal cells to choreograph the syntactical structures of externally controlled and internally generated neural sentences.

The Size of Cell Assemblies—a Hierarchy of Importance

Do neuronal assemblies more resemble quartets, chamber orchestras, or large philharmonic orchestras? In Hebb's cell assemblies, membership is defined by connectedness through excitatory synapses (Figure 1A). However, as discussed above, neither a sufficient nor a total number of assembly members can be determined without knowing the timeframe and the goal. Since the reader-centric definition of the assembly depends on classifier mechanisms, the question of assembly size should also be approached from this perspective. As discussed above (Figure 2), if the goal of an assembly is to discharge a downstream pyramidal cell in vivo, the number of neurons whose spikes can be integrated in approximately 20 ms (i.e., one gamma cycle) can quantitatively define the size of the effective assembly. Since approximately 1% of hippocampal pyramidal cells fire in a 20 ms time window during theta-related behaviors (Csicsvari et al., 1998, 1999), and 15,000 to 30,000 CA3 pyramidal cells converge on a CA1 pyramidal neuron (Li et al., 1994; Megias et al., 2001), these relationships indicate that, on average, 150 to 300 CA3 pyramidal cells firing within a gamma cycle comprise an assembly (de Almeida et al., 2007), a number similar to the estimate in HVC of the zebra finch (Hahnloser et al., 2002). Under special conditions, when the inputs converge on the same dendritic branch and fire synchronously in < 6 ms, as few as 20 neurons may be sufficient to initiate a forward-propa-

gating dendritic spike (Losonczy and Magee, 2006). These conditions may be present in the hippocampus during sharp wave ripples (Csicsvari et al., 2000) and in the geniculocortical system during visual transmission (Wang et al., 2010).

In a different approach to estimate the minimum number of spiking neurons to effectively substitute the effect of a sensory input, channelrhodopsin-2 (ChR2)-expressing neurons in the motor cortex were directly stimulated by light. Mice could detect the occurrence of single action potentials in approximately 300 synchronously active neurons. Even fewer neurons (~60) were required when the light induced a train of spikes (Huber et al., 2008). Under special conditions, stimulation of a single pyramidal cell or interneuron can recruit a large fraction of neurons in the circuit (Miles, 1990; Bonifazi et al., 2009; Ellender et al., 2010). Intense trains of intracellularly evoked spikes in a single motor cortex neuron were sufficient to evoke or reset whisking movement in the rat (Brecht et al., 2004). However, in these studies the directly discharged neurons probably activated an unknown number of other cells, and without monitoring of the entire population the number of neurons that generated the desired behaviors has remained unknown.

An inherent difficulty in determining the size of a neuronal assembly is that without an explicit goal, it is not possible to quantitatively define which neurons belong to the primary assembly and which represent feedback activation of assembly members or newly recruited assemblies, serving other goals. Although many neurons can contribute to a cell assembly, the contribution of individual members is most often strongly skewed, as is the case for musical orchestras. For example, activity of just a few strongly firing hippocampal place cells can be much more informative about the rat's position than several dozens of simultaneously recorded other neurons from the same volume and with the same total number of spikes (Wilson and McNaughton, 1993). Similarly, neurons that can predict the future choice of the animal in the hippocampus and prefrontal cortex represent only 1% to 10% of the recorded active cells, yet they are more informative about the behavioral outcome than the entire remaining population (Ferbinteanu and Shapiro, 2003; Frank et al., 2000; Fujisawa et al., 2008; Pastalkova et al., 2008; Quiroga et al., 2005; Wood et al., 2008). In the olfactory bulb, fewer than 10% of sharply tuned reader-classifier mitral cells are responsible for generating discrete and defined outputs, even though a large fraction of neurons contribute some spikes (Niessing and Friedrich, 2010).

BMI studies, where the reader mechanisms required to control an actuator are well defined by the experimenter, also support the view that assembly member contribution is nonisotropic (Fetz, 2007). Multiple laboratories have reported that the most informative subset of 10 to 20 task-related motor cortex neurons can predict as much as 60% to 80% accuracy of limb position or gripping force, and adding further information from the remaining several dozens of simultaneously recorded neurons from either the motor cortex or other areas improve the prediction only by a modest 10% to 15% (Figure 5B; Carmena et al., 2003; Hochberg et al., 2006; Serruya et al., 2002; Taylor et al., 2002; Wessberg et al., 2000; cf., Nicolelis and Lebedev, 2009). A similar hyperbolic relationship between the number of CA3 neurons and the occurrence of CA1 “ripples” (“reader pattern”)

has been described in the hippocampus (Csicsvari et al., 2000). The diminishing returns obtained from increasing the assembly size in achieving target control in BMI studies can be interpreted in two different ways: first, that coordinated activity by a few or perhaps dozens of neurons comprises an assembly, which can be regarded by a reader mechanism as “good enough” (Fetz, 2007; Serruya et al., 2002); alternatively, if the goal is to achieve 100% accuracy of performance each time, then spiking information from very large numbers of neurons in multiple related brain areas may be needed (Nicoletis and Lebedev, 2009).¹⁷

The challenges in objectively determining the size of the assembly, neuronal word, or sentence, which can lead to an observable output, include not only recording large numbers of neurons simultaneously but also determining the critical brain areas, cortical layers, and neuron types that are most relevant in producing the desired output. Adding more neurons from structures not critical for the task would artificially reduce the estimated fraction of participating cells. Finally, if the network in which the assembly is embedded has scale-free features, the assembly size may scale with the network, rather than represent an “optimal” size (Sporns et al., 2007). To date, we can only tentatively conclude that even a small cell assembly in the cortex probably involves tens to hundreds of pyramidal cells and their transient partner interneurons but the exact size depends on the required accuracy of the goal. It appears then that while the cell assembly can be conceived of as a large philharmonic orchestra in which the contribution of each instrument is needed to perform a perfect concert, a small fraction of key assembly members can play a “good enough” recital.

Reading Cell Assemblies and Assembly Sequences

Neural messages are only as useful as their readability. Complex assembly sequences acquire meaning only through appropriate reader mechanisms, which can reliably differentiate among the multiple overlapping sequence patterns. While establishing a correlation between various sensory inputs and firing patterns is an important step in brain research, the biological relevance of these statistics-derived “representations” can be verified only through some actuator mechanism. Multiple time-integrator (reader) mechanisms exist in the brain, each with a characteristic temporal window, and integrators with longer time constants can combine neural assemblies into long sequences. Different reader mechanisms may simultaneously monitor the activity of the same assembly patterns and may extract different types of meanings, for example temporal relationships for one feature and spiking intensity for another (Hirase et al., 1999; Huxter et al., 2003; Konishi, 1990; Niessing and Friedrich, 2010).

To date, very little experimental evidence is available regarding the exact mechanisms that allow readers to segregate complex trajectories (MacLeod et al., 1998). In the simplest case, a particular temporal pattern of neurons converges on a given reader neuron because of the hard-wired features of a circuit. This simple but nonrealistic example assumes that the readers are in a constant “alert” state, ready to integrate. In a more realistic situation, the readers may be influenced by other inputs as well (e.g., subcortical neuromodulators); therefore, their pattern segregating may be strongly influenced by the state of the neural network. To forge a special relationship between readers and

their assemblies, words, or sentences, further learning or selection rules, which can bring about long-term modification of the relationship between neurons, may be needed. Synaptic plasticity, particularly spike-timing-dependent plasticity (Levy and Steward, 1979; Magee and Johnston, 1997; Markram et al., 2007), is often exploited in computational models to modify circuit connections. The learning process may be facilitated by some supervisory mechanism and/or feedback-modifying mechanisms. Supervision can simply mean just a time constraint, such as oscillation-induced silencing of readers and their potential upstream assemblies, or it can refer to other complex top-down effects, which a priori allow some combinations and disallow others. Alternatively, the reader’s ability to identify a unique upstream constellation of neuronal patterns can be strengthened by reinforcers (i.e., goals), which optimize the connectivity of the upstream assembly post-hoc so that it will activate the reader more effectively on future occasions (Izhikevich, 2007; Legenstein and Maass, 2007; Maass et al., 2002; Seung, 2003). If multiple readers send their outputs to a downstream integrator/reader, the readers in the input layer become assembly partners from the perspective of the downstream reader (Figure 1C).¹⁸ In turn, the links between the “hidden layer” readers (Rumelhart and Zipser, 1986) may be modified by any of the above mechanisms. Although neither the generality nor the biological viability of these hypothetical selection processes is firmly supported by physiological data, the reader-centric perspective of assembly organization provides a disciplined framework to uncover the mechanisms that enhance the relationship between upstream firing patterns and the readers of such patterns.

Simple computational models, using reverse correlations (e.g., Berry et al., 1997; deCharms et al., 1998), can illustrate the pattern classification abilities of reader/actuator mechanisms (Rumelhart and Zipser, 1986). Various population patterns generated by a network of model neurons can evoke spiking responses in one or just a few reader cells. A given reader neuron or assembly of readers can respond to a random pattern of neuronal discharge in the input layer, and during the learning process it becomes selective to it and only to it. Thus, only a specific pattern becomes meaningful to this reader. To provide biological meaning to a second pattern, another reader, selectively tuned to the second pattern, is needed (Figure 1C). Learning to discriminate numerous patterns requires increasing numbers of selective readers (Masquelier et al., 2009). For example, the 50,000 reader KCs in the mushroom body, in principal, can respond to 50,000 odorant combinations (Figure 3A; Jortner et al., 2007; Perez-Orive et al., 2002). Discriminating between two trajectories (assembly sequences) of hippocampal or prefrontal neurons by downstream readers, corresponding to two different choices, is a relatively simple task (Figure 4). On the other hand, segregating large numbers of trajectories, representing all episodes collected in one’s lifetime, requires complex mechanisms with many dedicated readers. Such system of readers with the ability to effectively orthogonalize upstream patterns, is exemplified by the strong divergence of the entorhinal cortex-dentate granule cell connectivity and the sparse responses of granule cells (Jung and McNaughton, 1993; Leutgeb et al., 2007).¹⁹ On a larger scale, the entire neocortex can

be conceived as a segregating orthogonalizing layer, with its reader mechanisms learning to classify and segregate overlapping hippocampal output patterns and lay them down as memories (McClelland et al., 1995) or translate them to plans and overt behavioral responses.

In addition to their current input connectivity vector, readers may be also sensitive to the preceding states of the assembly sequence (Figure 3B; Gütiğ and Sompolinsky, 2006; Truccolo et al., 2010). As discussed above for BMI actuators, extracting the most accurate information about, e.g., arm position, is a daunting task when the statistical classifier mechanisms have to monitor a high-dimensional sample of the active state of neurons. In contrast, computational considerations suggest that the high-dimensionality of the input vector, in fact, can often facilitate the extraction of information by neuronal readers (Cover, 1965; Haeusler et al., 2003; Maass et al., 2002; Pulvermüller and Knoblauch, 2009), and separation of trajectories becomes progressively easier with increasing dimensionality of state space (Legenstein and Maass, 2007; Legenstein et al., 2010; c.f., Buonomano and Maass, 2009). This may explain why natural readers, such as neurons, have a high flexibility and can adapt to very subtle differences between neuronal trajectories (Fetz, 2007; Logothetis and Pauls, 1995; Poggio and Edelman, 1990). These examples indicate that extracting useful information from temporally evolving neuronal trajectories of long series of assemblies by statistical means may be a more formidable task than separating different neuronal trajectories by the response patterns of reader-decoder mechanisms (Laurent, 1999)²⁰ because of their ability to drastically reduce the dimensionality of information streams (Nessler et al., 2010).

Reader-Initiated Transfer of Neuronal Messages

Transfer of messages from source (sender) to target (reader) is usually considered a unidirectional operation: the source sends the information to an ever-ready recipient network. Brain networks do not appear to work this way. Instead, the reader plays the initiating role by temporally biasing activity in the source networks and creating time windows within which the reader can most effectively receive information (Figure 10; Sirota et al., 2003, 2008). Each sensory system has coevolved with such a reader-initiated transfer mechanism. Dedicated motor outputs, such as saccadic eye movements, licking, sniffing, whisking, touching, twitching of the inner ear muscles, or other gating mechanisms assist their specific sensory systems by “resetting” or synchronizing spiking activity in large parts of the corresponding sensory system and/or creating transient gains, which enhance the reader (sensory) system’s ability to process the inputs (Ahissar and Arieli, 2001; Bremmer et al., 2009; Gutierrez et al., 2010; Halpern, 1983; Henson, 1965; Kepecs et al., 2006; Kleinfeld et al., 2006).

Neuronal networks in the inner parts of the brain have also adopted reader-initiated mechanisms for transient gains. For example, transfer of hippocampal information to the neocortex (the “reader”) during slow-wave sleep can be initiated by the down-up transition of the neocortical slow oscillation (Buzsáki, 1998; Isomura et al., 2006; Sirota and Buzsáki, 2005; Sirota et al., 2003), which can bias the spike content of hippocampal

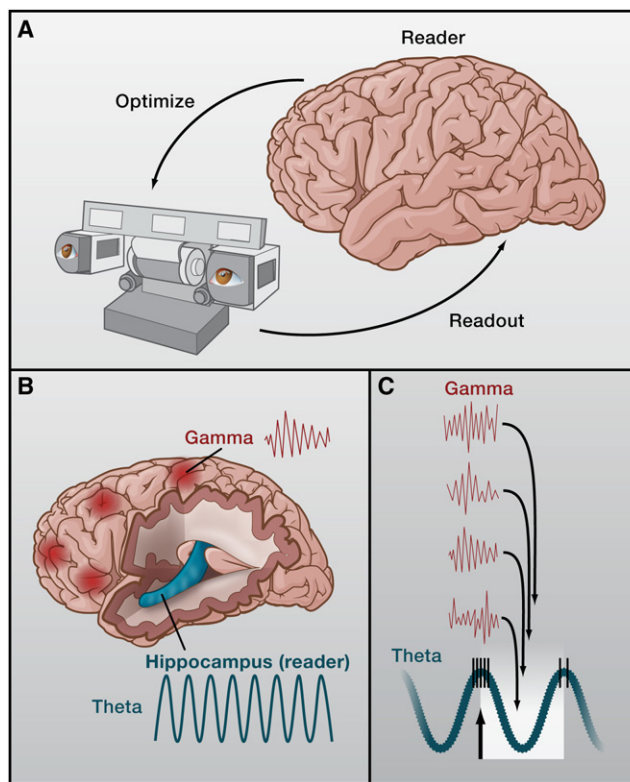


Figure 10. Reader-Initiated Transfer of Information

(A) The reader sends an output command to optimize the sensor. Brain-initiated synchronizing-blanking mechanisms are used in all modalities (such as eye movement, sniffing, whisking, active touch, licking, contraction of middle ear muscles, etc.), which generate transient “gains.” (B) Reader-initiated transfer is used at all levels of the brain. In this example, the hippocampus (reader)-generated theta oscillation synchronizes computations in widespread neocortical areas (reflected by transient gamma oscillations). (C) The duty phase of hippocampal theta (white arrow) biases the timing of neocortical circuits so that the results of the local computations are presented to the reader during the accrual (“readiness”) phase of the oscillation.

sharp wave ripples (Battaglia et al., 2004; Ji and Wilson, 2007). In the waking brain, the direction bias works in the opposite direction. Now the dialog is initiated by the hippocampus via theta-phase control of neocortical network dynamics (Sirota et al., 2008). As a result, the content of the temporally biased, self-organized gamma oscillations at multiple cortical locations can arrive to the hippocampus at the phase of the theta cycle when hippocampal networks (the “reader”) are in their most sensitive, plastic state (Figure 10B; Huerta and Lisman, 1996). Exchange of information between different stages of the visual system appears to follow similar rules (Fries, 2005; Womelsdorf et al., 2007), implicating a general rule for the reader-initiated transfer of neural messages.²¹

Mimicking and Perturbing Cell Assemblies, Neural Words, and Sentences

Event A is believed to cause event B if it regularly precedes B in time and if in its absence B fails to occur. Thus, while the activity of a reader-actuator (event B) may regularly follow a unique

trajectory of assemblies (event A), providing circumstantial evidence for a cause-effect relationship, definite evidence requires either artificial recreation or elimination of the cause (event A). Since methods for selective and fast activation and inactivation of multiple single neurons and synapses by light activation are on the horizon (Boyden et al., 2005; Deisseroth et al., 2006; Luo et al., 2008; Miesenböck, 2009; Zhang et al., 2007), discussion of their potential use in identifying assemblies, neural words, and sentences is warranted.

Knowledge of the regular features about the spatiotemporal patterns of spiking behavior in an assembly could be used to recreate those patterns artificially and examine whether such synthetic assembly patterns evoke similar behaviors as the native ones (c.f., Cohen and Newsome, 2004). In principle, this approach could provide the long-awaited mechanistic understanding of cell assembly organization (c.f., Luo et al., 2008; O'Connor et al., 2009). It may also help extract the essential features of assembly activity, such as the minimum assembly size, the required temporal precision, and the sequential recruitment effects. While this approach should be attempted, it may not always work effectively. A failure to elicit the desired effect may occur for various reasons. For example, the required assembly to be activated may reside in multiple structures and activation of neurons in a single structure may not be sufficient. Even if one manages to activate all neurons, the imposed synthetic pattern has to compete with an ongoing program because neuronal networks in the brain are spontaneously and perpetually active. The meaning of an artificial pattern for the same reader in the context where the native assembly pattern was originally observed or, say, during sleep therefore might be fundamentally different. Ideally, the imposed pattern should be embedded in the same mesoscopic temporal dynamic as the observed one. This may be facilitated, for example, by detecting LFP or firing patterns of neurons and using their phase or other features for proper timing of the synthetic pattern.

A practical challenge for the successful application of the synthetic assembly method is to selectively activate neurons. This would require an a priori knowledge of the spatiotemporal pattern of the assembly members and selective light delivery only to these member neurons in the appropriate temporal order. Currently used “optrodes” are not up to this task because light is delivered to orders of magnitude more neurons than the few observed (Cardin et al., 2009; Han et al., 2009; Sohal et al., 2009; c.f., Miesenböck, 2009). More localized delivery of light limited to the volume of recorded neurons is a necessary requirement to this end (Royer et al., 2010b). An alternative solution is to express light sensitivity in those neurons only that are active in a given specific task and test whether their subsequent activation elicits the same behavior. While such activity markers may identify the members of neural words (Claridge-Chang et al., 2009), appropriate temporal sequencing may still be necessary since different temporal ordering of the same assemblies may be interpreted differently by the reader-actuator. Finally, even successful elicitation of a desired behavior should also be interpreted with caution because in situations with a limited repertoire of choices many stimulus patterns may elicit the same (or the only available) choice.

Silencing the presumed members of an assembly, normally causally related to an event, may not lead to the absence of an effect. For example, temporary or even permanent silencing of “Halle Berry neurons” in the hippocampus and associated structures (Quiroga et al., 2005) may not erase the semantic representation of the actress. The reason is that specific firing of these explicit neurons (“grandmother cells”; Barlow, 1972) is a result of a dynamic and hierarchical relationship between winner neurons and their transiently inhibited competing peers. Elimination of winners may be instantaneously replaced by runner-up neurons.

An alternative strategy to native pattern replication or transient neuron elimination for studying cell assemblies is to systematically perturb the online monitored native pattern or part of it. For example, properly timed discharge of weakly connected neurons may strengthen their connections and incorporate them into the assembly sequence (Dragoi et al., 2003; King et al., 1999). Conversely, appropriately timed silencing of assembly members may eliminate them from future attendance in the assembly. An equally promising direction is the temporal jittering of spikes by applying statistically defined noise. While temporal jittering of spikes can maintain firing rates and the average spiking behavior of neurons, it can be used to probe the reader's tolerance for interpreting the relevant information. For studying the behavioral impact of such manipulations, the obvious challenge is to jitter spikes in a large enough volume of neuronal tissue selectively. In addition to engineering efficient optogenetic methods, drugs affecting short-term synaptic plasticity, but less so firing rates, can be used to probe circuits. For example, drug activation of presynaptic cannabinoid receptors (Freund et al., 2003) had no effect on the positional representation of hippocampal place cells, field size, or their population vector, thus leaving the “spatial map” intact, yet the rats could not solve a spatial task. Since the drug interfered with the timing of neuronal spikes at the gamma-theta timescale, the behavioral impairment may be explained by the inability of the reader mechanisms to properly interpret the hippocampal messages (Robbe and Buzsáki, 2009).

Analysis of synapsesembles requires specific manipulations of the connectivity between different neurons types (von Engelhardt et al., 2010; Wulff et al., 2009). Synapsesembles can be also targeted by fast optical means (Wang et al., 2007; Szobota et al., 2007) so that transitions from words to words can be affected. While it is impossible to be prophetic in this fast developing area of research (O'Connor et al., 2009; Miesenböck, 2009), it is likely that the combination of large-scale multiple single-neuron recordings and application of a whole family of perturbation methods will open new possibilities for understanding the content and meaning of assemblies and their sequential organization.

In addition to these invasive and complex methods, studying the temporal evolution of LFPs and other collective features of neurons can provide insights into the organization of neural syntax. If gamma waves or measures of population activity do in fact reflect the fundamental assemblies of the syntax, examining the time course of gamma power and its modulation by the phase of the slower alpha, theta, and delta rhythms may be a promising direction in human subjects even if the semantic

content shaped by the neural syntax remains invisible (Bastiaansen et al., 2002, 2009; Jacobs and Kahana, 2009; Steinvorth et al., 2010). Interpreting mesoscopic signals will require further exploration since the frequency of LFP gamma transients and their coupling across layers and cortical “modules” vary as a function of behavior (Colgin et al., 2009; Montgomery and Buzsáki, 2007; Sirota et al., 2008). With appropriate methods the temporal dynamics of neuronal recruitment and their LFP reflections can be accelerated or slowed down and their impact on the reader mechanism evaluated (Long and Fee, 2008). One can only speculate that the roots of language and musical syntax do in fact emanate from the neural syntax native to the brain (Pulvermüller, 2010), since it is the neural syntax that secures a match between brains, which both generate and interpret information.

SUPPLEMENTAL INFORMATION

Supplemental Information includes the notes for this manuscript and can be found with this Review online at doi:10.1016/j.neuron.2010.09.023.

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