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Neuron

Meeting Report

Emerging principles of spacetime in brains: Meeting report on spatial neurodynamics

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https://doi.org/10.1016/j.neuron.2022.05.018

SUMMARY

How do neurons and networks of neurons interact spatially? Here, we overview recent discoveries revealing how spatial dynamics of spiking and postsynaptic activity efficiently expose and explain fundamental brain and brainstem mechanisms behind detection, perception, learning, and behavior.

INTRODUCTION

Traditionally, dynamics mean changes in a system evolving over time. Neurons interact by sending action potentials propagating along axons to release transmitters inducing postsynaptic currents in target neurons locally and at distant locations in the central nervous system. This fundamental mechanism thus creates *spatial* dynamics in the large network that makes up a central nervous system. Spatial dynamics can be captured by multiple simultaneous, multi-region, electrophysiological or optical recordings and, more recently, by cellular neuroimaging. The authors of this summary met in the first spatial neurodynamics (virtual) workshop to discuss results from such recordings and find principles for spatial interactions of neurons. We define ''spatial neurodynamics'' as the part of neuroscience examining how changes in emission of action potentials, other membrane currents, transmitter synaptic releases, and receptor-induced biochemical cascades propagate through the network of neurons that makes up a central nervous system. Neurons interact with shifting partners over shifting distances with shifting delays. Consequently, spatial dynamics is not the sum of the temporal dynamics of neurons firing at different positions during a task.

In this meeting report, we discuss experimental examples of spatial neurodynamics in zebrafish larvae, rodents, and primates presented by the speakers. The data revealed interactions between neurons in the cerebral cortex, basal ganglia, thalamic, and brain stem nuclei, as well as emergent principles of spatial neurodynamics, which may transform systems neuroscience.

Behavioral conditions and brain mechanisms

As stated by David McCormick, how does a brain choose among all its local networks to get those necessary to interact? One answer was given by Li and Robson using the ideal experimental animal, the zebrafish larvae in which all its 80,000 neurons can be simultaneously studied (Marques et al., 2020). In this preparation, there is a causal relation between brain mechanisms and two behavioral states. The larvae have two fundamental behavioral states: exploration and exploitation. During exploration, they quickly swim around and explore most of their surroundings. During exploitation, larvae calmly observe prey and then make fine motor adjustments to hunt and catch the prey. A subset of trigger neurons (e.g., in the habenula) are phasically activated at the transition from exploration to exploitation (Marques et al., 2020). A tonic dorsal raphe signal then persists through the exploitation state. This change in raphe activity is correlated with widespread changes in sensorimotor responses in the optic tectum, cerebellum, and hindbrain. The spatiotemporal propagation of activity from phasically active trigger neurons to tonic activating state-encoding neurons in the dorsal raphe may be a general mechanism for state transitions in the brain. This study emphasizes the value of studying brain mechanisms generating spontaneous behavior, in contrast to more classical experimental paradigms. However, experimental studies are almost exclusively done by imposing a task and stimuli to the animal under controlled and behaviorally defined epochs.

Changes in activity before experimental trials start

Already from the moment a well-trained animal is put in the test apparatus, there is a particular ongoing spatial dynamic

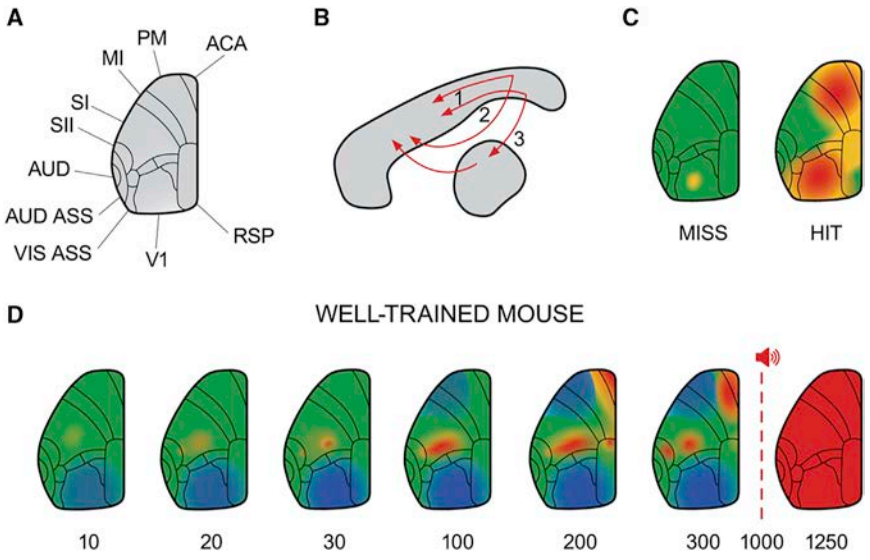

Figure 1. Spatial dynamics in cortical networks

(A) Dorsal view of the mouse cerebral cortex with areas.

(B) Fast propagation modes of spatial dynamics: (1) propagation can be intracortical, spreading along cortical layers (3 and 5) to adjacent areas 0.01–0.4 mm ms^{1}; (2) via cortico-cortical axons connecting cortical areas within 2–8 ms; or (3) via cortico-thalamo-cortical axons.

(C) Single trial example of a missed trial (left) and a hit (right) of a mouse detecting a faint luminance increase of an LED. GCaMP recording (modified after Salkoff et al., 2020).

(D) Well-trained mouse receives a weak deflection of one whisker at 0 ms but is not allowed to confirm the detection by licking until the auditory beep at 1,000 ms. After the beep, the intracellular Ca^{2+}i ncreases spread laterally and posteriorly to cover the cortex. RCaMP recording (modified after Esmaeili et al., 2021). ACA, anterior cingulate area; PM, premotor area; MI, primary motor area; SI, primary somatosensory area; SII, secondary somatosensory area; AUD, primary auditory area; AUD ASS, auditory association areas; VIS ASS, visual association areas; V1, primary visual area; RSP, retrosplenial area. Green baseline activity; yellow, orange, and red increase in intracellular Ca^{2+}; blue decrease in activity.

prior to the experimental trials. Kenneth Harris' group compared the spiking prior to trials in sessions in which mice were doing a well-learned task with the spiking prior to trials in sessions in which the mice were just exposed to visual stimuli. The pre-trial spiking in CA3 of hippocampus, the dentate gyrus, basal ganglia, zona incerta, substantia nigra, and the midbrain reticular formation correlated positively with this difference, signifying engagement in the experiment. Whereas the spiking of neurons in visual , somatosensory , primary motor , retrosplenial (RSP), anterior cingulate area (ACA) , and posterior thalamus (lateralis posterior [LP], pulvinar [P]nuclei) correlated negatively with the experimental engagement (Steinmetz et al., 2019).

Mice trained to detect a faint visual stimulus have a significant decrease of the Ca^{2+} signal of the pyramidal neurons in primary visual cortex occasionally combined with an increase in a visual association area at the start of experimental trials (Salkoff et al., 2020). Mice that were trained to detect a small change in an ongoing visual stimulus and were required to initiate trials by refraining from movements show anticipatory increase in activity in primary and secondary motor cortex (Orsolic et al., 2021). These pre-trial activations and de-activations are results of internal spatial dynamics, achieved by training, because they do not appear in untrained animals (Steinmetz et al., 2019; Salkoff et al., 2020; Orsolic et al., 2021). They fine-tune the excitability of key areas in advance of the experimental trial. Perhaps the subcortical structures positively correlated with experimental engagement may have a role.

These consistent findings turn attention to baseline and control conditions in experimental neuroscience. Baseline conditions are the null conditions, from which the task-induced changes in spiking are determined. Instead of random spiking, excitation, and inhibition, the adaptation to the experimental condition seems to induce highly organized "baseline" dynamics engaging cerebral cortex, basal ganglia, thalamus, and brain stem nuclei.

Spatial order of dynamics in cerebral cortex and basal ganglia during tasks

Several groups presented widefield (mesoscopic) recordings of the cerebral cortex with genetically encoded intracellular Ca^{2+} indicators, supplemented with multiple recordings of spiking to capture cortical spatial dynamics in well-trained mice performing complex tasks. The mesoscopic Ca^{2+} signal increases if the spiking or synaptic and dendritic activity of the encoded pyramidal neurons increase and decreases if this activity decreases.

Carl Petersen presented mice trained to detect a short deflection of one whisker. In successful trials, increases of spiking and intracellular Ca^{2+} progressed in the order SI, S II, premotor area (PM), ACA, and caudate nucleus (Esmaeili et al., 2021) (Figure 1). Similarly, Thomas Mrsic-Flogel and David McCormick presented data from mice trained in detecting visual stimuli or a change in an ongoing visual stimulus. In successful trials, Ca^{2} increases progress in the order V1, visual association area (VIS ASS), PM, ACA, and RSP (Salkoff et al., 2020; Orsolic et al., 2021). This cortical order is confirmed by increases in spiking during visual discrimination in the same areas but also subcortically approximately in the order superior colliculus, LP nucleus of thalamus, caudate nucleus, LD thalamus, zona incerta, and anterior pre-tectum (Steinmetz et al., 2019). These results show that spatial dynamics are real, reproduceable, and not limited to superficial cortical layers.

These tasks were divided into epochs in which the animal learns to express a specific behavior, which could determine the order of the activations. For example, when the mouse has detected the whisker deflection, it must wait for a tone to obtain the reward (licking water). If the mouse withholds licking and

moving during the delay period, the M1 motor neurons do not increase their spike rates until the auditory signal comes.

Failure of spatial dynamics to progress implies missed trials

David McCormick reported that the mouse failed to respond if the visual cortex was highly active prior to the visual stimulus. In addition, mice fail to respond when the Ca^{2+} signal does not spread further on to the visual association areas, the RSP, ACA, PM, and motor areas (Figure 1C) (Salkoff et al., 2020; Orsolic et al., 2021). Similarly, in missed trials, the Ca^{2+} signal and spiking in SI and SII (Figure 1D) does not progress further (Esmaeili et al., 2021). Failure of cortical spiking to progress beyond visual association areas and failure to progress subcortically beyond the dorsal striatum leads also to failure to respond in the paradigm of Steinmetz et al. (2019). By systematically inactivating neurons in different cortical areas during a task, three groups (Harris, Petersen, and Mrsic- Flogel) found causally correlated neurons with visual, auditory, and somatosensory sensation not only in visual, auditory, and somatosensory areas but also in the premotor cortex and midline prefrontal area (ACA) (Zatka-Haas et al., 2021; Esmaeili et al., 2021). So, the spatial spiking and postsynaptic Ca^{2+} dynamics relate causally to single trial success and failure.

Top-down spatial dynamics, spontaneous, and global engagement

Similarly, to the zebrafish larvae, mice can shift from exploration to exploitation. This can happen spontaneously or when the mouse goes for the reward.

When a mouse is sitting relaxed in the test apparatus, spikes appear seemingly random over the cortex at a slow rate. Spontaneously, the mouse can suddenly start running and whisking, which is associated with a global cortical Ca^{2+} increase starting in premotor cortex and propagating caudally increasing Ca^{2+} even in the primary visual cortex. In dual recordings from the dorsal lateral geniculate nucleus and V1, the membrane potentials of neurons show similar and phase-locked depolarizations to the onset of the whisking behavioral state with a lag less than 50 ms (Nestvogel and McCormick, 2022).

Similarly, when the mouse starts licking to obtain the reward, this often is combined with running and whisking. The Ca^{2+} increase starts in the premotor area or ACA and propagates caudally and laterally over some 200 ms all the way to V1 (Nestvogel and McCormick, 2022; Orsolic et al., 2021). All cortical areas and all subcortical structures except for the olfactory bulb and cortex contained neurons correlated with action initiation in the Steinmetz et al. (2019) study. This spontaneous global mouse brain dynamics offers an opportunity to reveal how a mammalian central nervous system organizes complex behavior.

Waves, sweeps, sharp waves, and spindles progressing in spacetime

Spatial dynamics of spiking and postsynaptic excitations and inhibitions in earlier studies done with voltage-sensitive dyes evolve at different spatial scales, in different directions, with different velocities, shapes, and amplitudes. Field potential waves propagating over the cortex is one example of larger-scale excitations, followed by inhibitions. In awake marmosets trained to detect a Gabor drifting target, the phase of the wave and spiking in area MT (visual middle temporal area) were time locked and predicted the likelihood of target detection (Davis et al., 2020).

Hippocampal sharp-wave ripples and their associated spike sequences are transferred to the retrospenial cortex (Figure 1A) during the retrieval of memory and during sleep (Abadshi et al., 2020; Esteves et al., 2021). These sharp waves and the associated spiking sequences spread over most of the cortex. The local depolarizations of the areas can lead or lag the sharp-wave ripple (Abadshi et al., 2020).

The key issue is the nature of neuronal communication between the hippocampus and neocortex. Communication is an agreement between the sender and receiver and needs a cipher known to each partner. In the brain, rhythms represent such ciphers. Spike sequences are composed by neurons that live in extended spatial networks. For example, theta phase-space-organized spiking during explorative behavior travels from the dorsal to the ventral tip of the hippocampus in half a theta cycle. During consummatory behaviors, including sleep, sharp-wave ripples show a more complex spatial travel pattern. At the same time, the neocortical target neuron networks also display complex spatial spindle and slow oscillation patterns. Thus, the experimental challenge is to demonstrate that these respective chaotic-appearing spatial network patterns in both the hippocampus and neocortex are, in fact, temporally coordinated; therefore, both code and decipher neuronal messages. As György Buzsáki expressed it, "time in the brain is a segment of neuronal space" (Buzsáki and Tingley 2018).

Terry Sejnowski presented spatial dynamics of sleep spindles in humans. Sleep spindles are thalamic 10–15 Hz oscillations in the local field potential spreading to the cerebral cortex, where they are thought to consolidate memory. In the human cerebral cortex, the spindles propagate as planar, circular, and spiral "waves" by 0.3 mm ms^{-1} or faster (Muller et al., 2016). Putative inhibitory neurons and putative excitatory neurons fired in phase with the spindles.

Spontaneously and during experiments, spiking progressing intra-cortically, cortico-cortically, and thalamo-cortically (Figure 1B) generate a variety mesoscopic and macroscopically coherent postsynaptic dynamics evolving in the large cortical network where space and time are inseparable. These are reproduceable mechanisms relating to what we insufficiently refer to as prediction, perception, retrieval and consolidation of memories, and specific behaviors.

New roles for the reticular formation and brain stem nuclei

Until now, the reticular formation of the brain stem and (matrix) neurons in thalamus were regarded as part of diffuse systems responsible for awakening, arousal, and maintaining consciousness but with no specific roles in perception, cognition, and planning of behavior. First, 10%–25% of neurons in substantia nigra, superior colliculus, pre-tectum, periacqueductal gray matter, zona incerta, and midbrain reticular formation correlate with action initiation. Second, neurons in nucleus accumbens, substantia nigra, zona incerta, and midbrain reticular formation are those strongest positively correlated with task engagement.

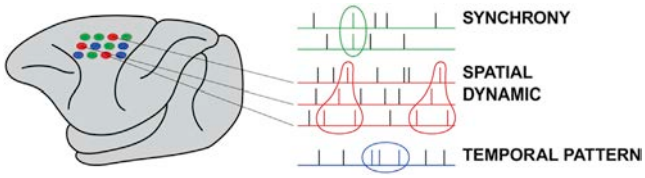

Figure 2. Spatial spiking dynamics

Cortical neurons organize in small groups of individual neurons spiking in the same order. Spikes recorded simultaneous from the premotor and motor cortex of awake behaving monkeys demonstrate that the same group of single neurons repetitively produce a sequence of spikes, always in the same spatial order (red). The spatial sequence is specific for the behavioral condition (Grün 2021). The neurons that are members of one spatial spiking sequence do not cluster in space. In the study, they were separated by at least 400 μm but typically more.

In the study by Steinmetz et al. (2019), the mouse turns a wheel to bring a visual target in to the center of field of view. Neurons in the parafascicular nucleus (pre-tectum), the zona incerta, and midbrain reticular formation fire just before and during a clockwise turn with the right forepaw. These neurons are those most correlated with the choice selection and fire reliably in every trial with no lag compared with the neurons in the premotor and motor cortex. In a similar study, human subjects press a response key with the right thumb if the luminance of a small visual target increases slightly. With the right index finger, they press another key if a somatosensory stimulus increases slightly. This task increases the regional cerebral blood flow significantly in the right midbrain reticular formation (Kinomura et al., 1996).

These studies of awake behaving mice and humans change the view of the midbrain reticular formation and its extension: the zona incerta. Here, neurons participate in concrete choices and fast motor control in complex tasks. This is a new perspective shifting the cortico-centric focus of systems neuroscience to that of interacting brain stem, cerebellar, basal ganglia, thalamic, and cortical networks.

Spatial spiking dynamics, a universal brain mechanism for single neuron interaction?

For years, neuroscientists examined spike trains from single neurons for special temporal patterns as signs of temporal codes or examined simultaneous recordings from two or more neurons to find synchrony in spike emission. Simultaneous recordings from many neurons tell another story. Sonja Grün and her group developed rigorous statistics to prove that the same spatial subset of neurons repetitively emits spikes in the same order (Stella et al., 2022). In the premotor and motor cortex of monkeys trained to reach and grasp, many subsets, comprising from 2 to 6 neurons each, repetitively emit from 2 to 6 spikes in the same order over many trials (Figure 2). There is thus a spatiotemporal order in the way spikes are emitted by different neurons, i.e., a true spatial dynamic of spiking. The jitter in the exact timing of the spikes is maximally 5 ms, which does not change the *spatial* order of the spikes. Furthermore, the spatial dynamical spike sequence is specific to the experimental behavioral condition (for example, cue, delay, preparation, reach, grasp, and hold). The same neuron can be a member of different spatial subsets. It is currently unclear whether the subset is composed of putative excitatory neurons or a mix of putative excitatory and inhibitory neurons.

Averaging across neurons or trials or different behaviors or even across a cortical area thus hides the underlying spatial dynamics. The spatial spiking dynamics discovered by Grün and associates showing how single neurons fire in spatial order is an original and fundamental insight in the collective behavior of single neurons, which opens for many future studies.

A look ahead

Many of the experimental results presented were not foreseen, whereas some have been predicted by theoretical studies. Our general conclusion is that spatial neurodynamics therefore seems a necessary complement to studies of temporal dynamics. The studies presented here elucidate how brains organize their spatial dynamics of spiking and postsynaptic changes at scales ranging from single neurons to macroscopic views. These dynamics relate to detection, prediction, perception, illusions, retrieval, and consolidation of memories. Learning to follow task instructions is associated with widespread spatial dynamics setting the stage for the trial-specific spatial dynamics. Failure of the trial-specific spatial dynamic to progress implies failure to respond. Learned activities depend on coordinated activities in large neuronal space, often involving the brainstem, hippocampus, basal ganglia, and neocortex. Just as behavior is holistic and integrated, so is the brain activity that generates it.

Spatial dynamics, experimentally and theoretically, is only in its infancy. Spike recordings tell which neurons change their spiking but not the spatial destinations or consequences of the spiking. This is now possible with fast voltage indicators. Observing the spiking from multiple neurons progressing through the low-dimensional geometry of brain networks is an obtainable goal. Spatial neurodynamics carries no theoretical or statistical assumptions. Unlike ‘‘traditional’’ neuroscience based on timeseries data and assuming point-to-point communication, we should strive to reveal spatial neurodynamics, the interactions among neurons at multiple spatial and temporal scales, preferably in single trials. After all, this is how brains work.

ACKNOWLEDGMENTS

This work was supported by a Lundbeck Foundation grant R255-2017-3665 to P.E.R. and H.L.

DECLARATION OF INTERESTS

G.B. is a member of the *Neuron* advisory board.

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