

# The brain from inside out

György Buzsáki

New York, NY: Oxford University Press, 2019

The brain has often been referred to as the final frontier for science. Many decades of excellent animal and human neuroscience research have revealed robust and often predictable patterns of single neuron and population neural responses to external stimuli, responses that are frequently modulated by internally driven information. Also, we can now reasonably and confidently predict the behavioral impact of damage to many brain areas. Does this mean that we understand *how* the brain processes behaviorally relevant information? In *The Brain from Inside Out*, György Buzsáki contends that an overreliance on cognitive psychology terms (such as attention, decision-making, and concepts of time) to drive behavioral and cognitive neuroscience research, and then interpret neural data, has stifled progress on this issue. In his view, this dependence has led to conclusions with little meaning since they (the cognitive concepts) are not grounded in neurobiology. That is, he argues, there is no ground truth for their existence. The traditional approach of selecting a psychological phenomenon, for example, attention, and then assuming that attention is coded somehow in the brain is referred to as the Outside-in view since the cognitive concept was first identified by intuition, and then assumed to be true, before we knew whether the brain actually carries out this function. Buzsáki predicts that heavy and continued reliance on the Outside-in approach will not result in significant progress toward answering the question of how the brain processes information that results in meaningful behaviors.

As an alternative view, Buzsáki proposes an Inside-out approach where one uses knowledge about the fundamental operating principles and constraints of local and global neural networks to then identify what the brain considers to be salient information and meaningful functions. Through a series of engaging chapters (often laced with entertaining anecdotes and personal stories), Buzsáki first takes the reader on a journey that starts with an explanation of the logical reasoning behind the Inside-out approach. This is followed by chapters that describe many details and thoughtful interpretations of cellular events within local and global neuronal assemblies, culminating in how these assemblies contribute to a self-organizing brain system that provides neurobiological grounding for the use of behavioral or cognitive concepts. Buzsáki then describes how external information and experiences become internalized in the brain, as well as how self-organized neural processing continues until internal thoughts are externalized into actions. Throughout the book, he strategically

weaves together philosophical and historical perspectives with landmark neuroscience discoveries to conclude that brains evolved to carry out a critical function for survival, and that is to predict the outcomes of actions. Thus, each brain comes equipped with a preexisting neural architecture that not only links but also continuously regulates activity across multiple scales (from synapses to local and global circuit interactions) via a self-organizing neural oscillatory system. This system naturally and continually generates sequences of neural activity over time (termed *neuronal trajectories*). Salient events that occur during activation of one of these trajectories might strengthen that particular trajectory which in turn enables it to be recalled at a later date. Other trajectories are not strengthened. The sequential information processing that is inherent within neuronal trajectories, then, by definition include past, present, and future information needed to make experience-dependent predictions. Overall, such an architecture is considered advantageous as it confers neural stability in the brain while also enabling much needed flexibility to process multiple types of information across time, information that will ultimately result in appropriate actions.

## 1 | THE BRAIN AS A PREDICTOR OF ACTION OUTCOMES

Many have suggested that, in the interest of survival, the brain has been sculpted through evolution so that action impacts subsequent sensation (e.g., Sperry, 1950), and this enables animals to predict as accurately as possible the outcomes of their actions (e.g., Llinás, 2001; Raichle, 2010). It is typically assumed that such statements refer specifically to overt behavioral acts since such actions and their consequences have been found to be strongly associated with distinct and temporally precise responses of neurons in many brain areas. According to the Inside-out view, “actions” should also include the outcomes of neural processing that do not involve overt acts, such as a thought or a recalled memory. Buzsáki discusses in a clear and accessible style the relevant principles of local and global network organization that enables structures like the hippocampus to critically contribute to the determination of future actions. He describes important features of hippocampal local circuit organization (e.g., the interplay between excitatory and inhibitory controls across scales of

functions, including ion channels, synapses, and rhythmic patterns of network activity) and the preponderance of log normal neuron properties that create the self-generating rhythmic system. The log normal properties skew and constrain how inputs are selected, and processed by, hippocampus. The brain's hierarchical organization of rhythmic neural activity ultimately determines how neuronal trajectory information generated in hippocampus is transmitted to and used by other brain areas, for example, the prefrontal cortex. His explanations are inclusive of known mechanisms of neural systems functions and neuroplasticity (e.g., Hebbian and homeostatic plasticity, spike timing-dependent plasticity, dendritic integration, degeneracy, the bias to processing information forward, and not backward, in time, phase precession, and hippocampal replay and preplay).

The Inside-out view effectively argues that since brains evolved to predict the outcomes of actions, our actions determine which information is deemed sufficiently salient to internalize. One might expect then that neuronal trajectories must somehow incorporate information about one's past, current, and future action state. Like many researchers, Buzsáki considers velocity coding by hippocampal neurons a proxy for action coding in hippocampus. It has yet to be determined, however, how past, current, and future actions are part of a velocity code. The Inside-out view also predicts that action information modulates the encoding of nonmovement information. Indeed, there are many demonstrations that an animal's velocity modulates the specificity of the nonmovement information. A classic example is the well-known impact of velocity on place fields (e.g., McNaughton et al., 1983). Generally, greater velocity of movement through a place field corresponds to stronger firing by a place cell, and thus presumably greater impact of that cell in a population response. Often such velocity correlations are interpreted as evidence that the hippocampus is essential for path integration, a type of navigation that is dependent on self-generated internal information (e.g., when visual cues are no longer available). Buzsáki's interpretation that velocity information is essential for hippocampus to link one's actions to consequences does not contradict the path integration interpretation, but rather his views provide a broader conceptual framework for understanding the meaning and uses of velocity information by hippocampal neurons.

Consistent with the Inside-out view, action state has indeed been shown to be a primary driver of neural activity across the brain. Velocity (presumably derived from motor efference copy) has been found to be a significant modulator of neural activity in many cortical and subcortical brain regions and for different types of movement, such as saccadic eye movements (e.g., Smalianchuk et al., 2018), intentional limb movements (e.g., Ashe & Georgopoulos, 1994), head movements (e.g., Kim et al., 2014), and whole body movements through space (McNaughton et al., 1983). While velocity coding seems to be common across the brain, different magnitudes of correlation are observed both within and across brain areas. For example, hippocampal place cells show correlations with velocity that are most commonly reported to range from about  $r = .25-.40$  (e.g., Eschenko & Mizumori, 2007; McNaughton et al., 1983). Similar ranges of velocity correlation have been described for other brain regions such as the striatum (e.g., Eschenko & Mizumori, 2007), parietal cortex (e.g., Chen

et al., 1994), perirhinal cortex (Lu & Bilkey, 2010), retrosplenial cortex (e.g., Vedder et al., 2017), and entorhinal cortex (e.g., Hinman et al., 2016; Kropff et al., 2015; Wills et al., 2012; Ye et al., 2018). Much stronger velocity correlations have been reported for midbrain structures like the lateral dorsal tegmentum, known to control dopamine cell firing in the ventral tegmental nucleus when animals perform the same task used for hippocampal recordings (correlation range was  $\pm 0.99$ ; Redila et al., 2015). *What is the significance of such a range of strengths of movement correlation if cells are merely receiving efference copy of motor commands?* Relatedly, while a correlation of 0.40 may be statistically significant, it is far from 100% which indicates that other information drives the firing of velocity cells. *What can account for observations of only partial correlations?* A number of explanations are possible. The absolute value of velocity correlations could simply be related to the number of synapses between the recorded cell and motor control structures or sensory input structures. The degree of velocity coding may be different across brain areas depending on the dynamic functions of the intrinsic local circuitry. Another (but non-exclusive) explanation may be that other inputs bias the strength of the velocity correlation perhaps depending on the task or environmental situation. As an example, memories that are recalled during task performance may impact velocity codes. Why should this happen? Perhaps, the memory contains information about the significance of past actions, and this may upregulate or downregulate the strength of motor efference in task-dependent ways. Buzsáki hints at this possibility when he states that with experience, action-oriented systems mature. *What does such a maturation process look like in the brain? Does the innate, self-organizing brain itself mature?* Many intriguing questions remain to be answered if we are to fully understand how action/action state information drives the selection of sensory information, how new inputs eventually become independent from action state information (as Buzsáki claims), and finally how organisms select appropriate responses.

As noted, velocity strongly modulates the in-field firing rates of place cells. This could be viewed as an example of action information (also known as velocity) defining salient sensory inputs (also known as location identification). A sequence of associated place fields (e.g., preplay events) may become stronger over time to enable accurate navigation to a predicted goal location. This scenario is consistent with the conclusion from the Inside-out view that the brain functions to link actions with outcomes to improve prediction accuracy. A different type of relationship with velocity, however, has also been reported, one for which an accounting by the Inside-out view is less clear. Ventral tegmental dopamine neurons (Puryear et al., 2010) recorded from maze-trained rats show reward-responsiveness that is similar to those described in studies with stationary primates (e.g., Schultz, 1998). Rat dopamine neurons responded with phasic excitation to reward encounters and inhibition to reward omission. Surprisingly, however, these same reward responsive cells were also shown to be velocity tuned when rats moved across the maze to collect the rewards. Given that the velocity and reward firing occurred at different times, and given that the velocity correlation was observed regardless of an animal's location or the location of imminent reward,

it is not clear how a particular outcome could be linked to a particular action in this case.

Further questions regarding the relationship between velocity correlations and action outcome is the demonstration that depending on the context or memory used to solve a task, a given cell can switch from being positively correlated with velocity to negatively correlated with velocity, or to showing no velocity correlate at all (e.g., Eschenko & Mizumori, 2007; Mizumori et al., 2007). How can this be explained with the Inside-out view? On the surface, it seems that these data indicate that motor efference copy is not a sufficient explanation for velocity correlations. The greater than expected variance in velocity correlations, and the context and memory dependencies of velocity correlated firing, suggests that the link between ongoing behaviors and neural codes is more complex than proposed. The present lack of accountability does not negate the Inside-out view. Rather it highlights core issues that could be addressed in the next phase of theory development so that we better understand how actions define the saliency of sensory inputs that are used to direct future actions.

## 2 | BOTTOM-UP VERSUS TOP-DOWN APPROACH

In science, distinctions are often made between bottom-up versus top-down approaches. If we can conveniently put one theory in one camp and a second theory into the other camp, then there is the implicit assumption that both are working on the same problem—just from different levels. While some may argue that the Inside-out view reflects a bottom-up approach and the Outside-in view reflects a top-down approach, it is worth noting that this is not the case since the Inside-out view argues that the brain comes with a pre-existing self-organizing and self-perpetuating set of neural elements whose interactions are constrained by the nature of the biophysical properties of the neural elements and networks of the brain. The log normal bias of most if not all neural properties is what seems to generate the iterative self-perpetuating nature of information processing, as well as define stimulus saliency. The existence of a predefined neural structural and functional organization is not consistent with a bottom up approach to neural or functional organization. Rather, when comparing the traditional Outside-in view, the Inside-out view should be considered a fundamentally and qualitatively different strategy for solving the problem of decoding the brain.

## 3 | LOOKING OUT FROM THE INSIDE

In *The Brain From Inside Out*, Buzsáki provides a compelling account of how brain circuitry and organization evolved to predict which actions lead to future goals, and why actions are needed to make sense of our world. Taking the Inside-out view requires a deep understanding of how the existing hierarchical neural architecture of the brain produces

a dynamic, self-sustaining system before assigning complex cognitive functions to the brain. Buzsáki concludes that evolution provides us with a brain whose organizational pattern at all levels (from ion channels to brain system oscillatory interactions) of neural activity results from highly skewed (nonegalitarian) processing of incoming information according to a predetermined, somewhat biased set of rules. This is a far cry from the more-or-less tabula rasa (blank slate) view that the brain passively accepts and then represents stimuli presented to it; an approach that Buzsáki argues is often taken by cognitive neuroscientists and computational modelers. Not surprisingly then Buzsáki arrives at a number of conclusions about the nature of information processing in the brain that are different from scientists using the Outside-in approach. As an example, Buzsáki spends a good portion of the book's real estate on the different views regarding the importance of time as a type of information that the brain cares about. He presents fascinating arguments from multiple scientific disciplines, from different cultures, and from philosophical and religious writings to conclude that the brain inherently processes information across time but it does not explicitly compute parameters of time such as duration. Outside-in researchers consider duration of time to be a fundamental type of information that the brain should care about, and thus they have been looking for its neural instantiation. Proponents of the Inside-out view do not believe that the brain selective identifies and process duration information.

Going forward, the Inside-out view is expected to continue to generate new hypotheses about what constitutes salient information for the brain and why. A challenge for the Inside-out view, however, is to resist as much as possible from imposing established cognitive terms on neural phenomenon as they may very well carry with them implicit assumptions of functions. As an example, to help the reader to appreciate the complexity of dynamic brain functional organization, Buzsáki cleverly makes the analogy between neural organization and language organization, often assigning linguistic terms to specific neural properties. Such an analogy is a potentially useful rubric for helping readers to understand complex concepts that define neural architecture. However, it remains to be seen if this is the best unbiased descriptor, one that does not inadvertently introduce and impose cognitive functions, an approach that could be construed as taking the Outside-in view.

As Buzsáki states in his book, the brain is an interdependent society of its elements—neurons—which are linked in dynamic and experience-dependent ways. To fully appreciate how this society adaptively moves forward, much work is still needed to identify, and then value, the contributions of the rich diversity of brain elements, as well as how the biased neural architecture incorporates diverse inputs. *The Brain from Inside Out* is an outstanding book that should be recommended readings for all students of neuroscience, regardless of one's career stage. It will challenge the reader to recognize and acknowledge their assumptions about brain and behavior relationships. With more experiments, it is expected that ultimately some cognitive constructs will be validated (i.e., found to be grounded in neurobiology) while others will not. In this way, the Inside-out and the Outside-in views can work together to uncover the secrets of the brain so that we can better understand our minds.

**ACKNOWLEDGMENT**


This work was supported by the National Institute of Mental Health under grant No. MH119391.

**CONFLICT OF INTEREST**

The author declares no conflict of interest.

**DATA AVAILABILITY STATEMENT**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Sheri J. Y. Mizumori 

Department of Psychology, Program in Neuroscience, University of  
Washington, Seattle, Washington  
Email: mizumori@uw.edu

**ORCID**

Sheri J. Y. Mizumori  <https://orcid.org/0000-0003-0240-2188>

**REFERENCES**

- Ashe, J., & Georgopoulos, A. P. (1994). Movement parameters and neural activity in motor cortex and area 5. *Cerebral Cortex*, 6, 590–600. <https://doi.org/10.1111/j.1749-6632.1993.tb22968.x>
- Chen, L. L., Lin, L. H., Green, E. J., Barnes, C. A., & McNaughton, B. L. (1994). Head-direction cells in the rat posterior cortex. I. Anatomical distribution and behavioral modulation. *Experimental Brain Research*, 101, 8–23. <https://doi.org/10.1007/BF00243212>
- Eschenko, O., & Mizumori, S. J. Y. (2007). Memory influences on hippocampal and striatal neural codes: Effects of a shift between task rules. *Neurobiology of Learning and Memory*, 87, 495–509. <https://doi.org/10.1016/j.nlm.2006.09.008>
- Hinman, J. R., Brandon, M. P., Climer, J. R., Chapman, G. W., & Hasselmo, M. E. (2016). Multiple running speed signals in medial entorhinal cortex. *Neuron*, 91, 666–679. <https://doi.org/10.1016/j.neuron.2016.06.027>
- Kim, N., Barter, J. W., Sukharnikova, T., & Yin, H. H. (2014). Striatal firing rate reflects head movement velocity. *European Journal of Neuroscience*, 40, 3481–3490. <https://doi.org/10.1016/j.nlm.2006.09.008>
- Kropff, E., Carmichael, J. E., Moser, M. B., & Moser, E. I. (2015). Speed cells in the medial entorhinal cortex. *Nature*, 523, 419–424. <https://doi.org/10.1038/nature14622>
- Llinas, R. R. (2001). *I of the vortex: From neurons to self*. Cambridge, MA: MIT Press.
- Lu, X., & Bilkey, D. K. (2010). The velocity-related firing property of hippocampal place cells is dependent on self-movement. *Hippocampus*, 20, 573–583. <https://doi.org/10.1002/hipo.20666>
- McNaughton, B. L., Barnes, C. A., & O'Keefe, J. (1983). The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Experimental Brain Research*, 52, 41–49. <https://doi.org/10.1007/BF00237147>
- Mizumori, S. J. Y., Smith, D. M., & Puryear, C. B. (2007). Hippocampal and neocortical interactions during context discrimination: Electrophysiological evidence from the rat. *Hippocampus*, 17, 851–862. <https://doi.org/10.1002/hipo.20317>
- Puryear, C. B., Kim, M. J., & Mizumori, S. J. Y. (2010). Conjunctive encoding of reward and movement by ventral tegmental area neurons: Contextual control during adaptive spatial navigation. *Behavioral Neuroscience*, 124, 234–247. <https://doi.org/10.1037/a0018865>
- Raichle, M. E. (2010). Two views of brain function. *Trends in Cognitive Science*, 14, 180–190. <https://doi.org/10.1016/j.tics.2010.01.008>
- Redila, V., Kinzel, C., Jo, Y. S., Puryear, C. P., & Mizumori, S. J. Y. (2015). A role for the lateral dorsal tegmentum in memory and decision neural circuitry. *Neurobiology of Learning and Memory*, 117, 83–108. <https://doi.org/10.1016/j.nlm.2014.05.009>
- Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, 80, 1–27. <https://doi.org/10.1152/jn.1998.80.1.1>
- Smalianchuk, I., Jagadisan, U. K., & Ghandi, N. J. (2018). Instantaneous midbrain control of saccade velocity. *Journal of Neuroscience*, 38, 10156–10167. <https://doi.org/10.1523/JNEUROSCI.0962-18.2018>
- Sperry, R. W. (1950). Neural basis of the spontaneous optokinetic response produced by visual inversion. *Journal of Comparative and Physiological Psychology*, 43, 482–489.
- Vedder, L. C., Miller, A. M. P., Harrison, M. B., & Smith, D. M. (2017). Retrosplenial cortical neurons encode navigational cues, trajectories and reward locations during goal directed navigation. *Cerebral Cortex*, 27, 3713–3723. <https://doi.org/10.1093/cercor/bhw192>
- Wills, T. H., Barry, C., & Cacucci, F. (2012). The abrupt development of adult-like grid cell firing in the medial entorhinal cortex. *Frontiers in Neural Circuits*, 6, 21. <https://doi.org/10.3389/fncir.2012.00021>
- Ye, J., Witter, M. P., Moser, M. B., & Moser, E. I. (2018). Entorhinal fast-spiking speed cells project to the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, 115, E1627–E1636. <https://doi.org/10.1073/pnas.1720855115>