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Previews

Time and experience are independent determinants of representational drift in CA1

J. Quinn Lee[1] and Mark P. Brandon[1,2,*]
[1]Department of Psychiatry, Faculty of Medicine, Douglas Hospital Research Centre, McGill University, Montreal, Canada
[2]Integrated Program in Neuroscience, Faculty of Medicine, McGill University, Montreal, Canada
*Correspondence: mark.brandon@mcgill.ca
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In this issue of *Neuron*, Khatib et al.[1] and Geva et al.[2] present complementary and breakthrough discoveries demonstrating that elapsed time and active experience independently affect unique aspects of representational drift in the hippocampus.

Memories, much like ripples on a pond, can appear distinct and vivid when fresh, but over time, their contours blur. Yet, we retain the ability to recall the essence of our memories, navigating our lives through the maps etched in our minds. This divergence between precision and persistence creates a fascinating paradox at the heart of our understanding of memory. Traditionally, the hippocampus—a brain region essential for episodic memory—has been viewed as a reliable cartographer, with a map-like representation of space believed to remain stable over weeks and even months. However, a landmark paper from Ziv et al.[3] challenged this view, when the authors demonstrated the phenomenon of "representational drift" in the hippocampus, in which map-like representations of space progressively change over time, such that hippocampal maps of the same space differed dramatically when observed days or weeks apart (Figure 1A; also see Mankin et al.[4]). Since this discovery, representational drift has been demonstrated in distributed systems throughout the brain, such as those underlying vision, olfaction, navigation, and memory.[5] Importantly, the behavioral and mechanistic determinants of drift remain largely unknown. One central question of recent discussion has been how the passage of time versus the accumulation of experience determines representational drift.[5]

In this issue of *Neuron*, two pioneering studies from Khatib et al.[1] and Geva et al.[2] grapple with this question. Their investigations dissect the influences of time and experience on hippocampal representational drift and suggest that each act as independent effectors of long-term spatial representation.

Khatib et al.[1] present compelling evidence that representational drift on a short timescale (within-day) is driven by active experience rather than the mere passage of time in the mouse hippocampal subregion dorsal CA1 (dCA1). Specifically, they demonstrate that the amount of active exploration of a familiar environment strongly predicts the extent of representational drift observed in spatial mapping of dCA1 (Figure 1B). Critically, they also show that experience-dependent representational drift is independent of elapsed time. This elegant study underscores the dynamic nature of spatial representation in the hippocampus with particular emphasis on the role of contextual experience in representational updating, thereby challenging the view of representational drift as a result of merely passive forgetting.[1–5]

With a complementary approach, Geva et al.[2] examine how extended time and experience (days to weeks) impact long-term representational drift in dCA1. In a longitudinal study in mice, they quantified changes in spatial tuning and activity rates of large neural populations in dCA1 while mice explored two familiar environments across several weeks. Their findings reveal a striking double dissociation of time and experience on the hippocampal neural code: on one hand, the passage of time predicts changes to neuronal activity rates (Figure 1C), while on the other hand, active experience alters the spatial tuning of dCA1 neurons (Figure 1B). In keeping with Khatibi et al.,[1] they also show that changes in spatial tuning were context specific and independent of changes to activity rates. This dissociation of factors underlying representational drift at the behavioral level reveals the complex nature of this phenomenon and suggests that multiple, parallel mechanisms possibly contribute to drift.

Together, Khatib et al.[1] and Geva et al.[2] show that hippocampal representational drift is differentially affected by the passage of time and active experience. Importantly, this work motivates new avenues for exploration and questions for future research. From one broad view of future studies, we ask: how do (possibly independent) mechanisms at the synaptic level orchestrate representational drift?

Recent modeling of representational drift demonstrates that biologically plausible learning rules and simple neural architectures can express drift while maintaining representational organization for a given set of inputs (via similarity) across time and experience,[6] similar to recent experimental results.[7] Future modeling and experimental work should examine how representations can be preserved in such networks, specifically looking at the differences in synaptic updates that occur with active experience versus time. We imagine that passive mechanisms, such as molecular turnover or noise during synaptic updating, could cause drift across time (Figure 1C). Given that Geva et al.[2] demonstrate that active experience specifically predicts changes to spatial tuning in dCA1 (Figure 1B), modeling studies might explore instantiations of biologically plausible learning rules to this end. We anticipate that active experience could uniquely affect feedforward inputs to the hippocampus from upstream cortical

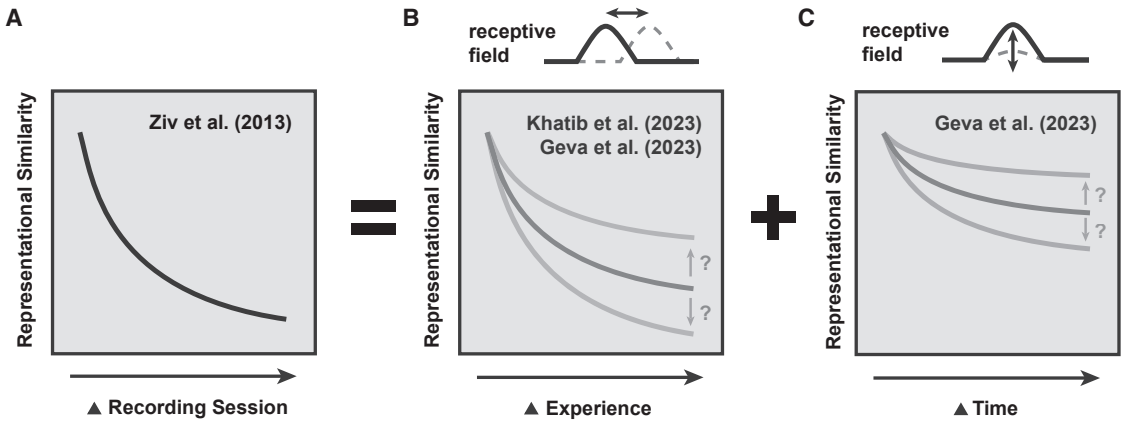

Figure 1. Experience and time distinctly affect representational drift

(A) A graphical summary of the classic representational drift observation,[3] wherein the similarity of representation decreases across sessions.

(B) Khatib et al.[1] and Geva et al.[2] show that experience causes drift within[1] and across days.[2] Specifically, this effect is driven by changes in neuronal tuning (receptive field above). We speculate that specific behavioral and plasticity functions could either increase or decrease the impact of experience on drift (arrows to different drift rates).

(C) Geva et al.[2] further show that protracted time differently impacts drift through changes in neuronal firing rates (receptive field above). Specific passive mechanisms might contribute to time-dependent representational drift (arrows).

structures (e.g., entorhinal cortex) via activity-dependent plasticity mechanisms, such as Hebbian learning.[6] While the observed experience-dependent effects[1,2] directly motivate these routes of investigation on possible synaptic mechanisms underlying drift, these findings also cast our attention to outstanding questions on how the dynamics of experience itself shape long-term representations.

Khatib et al.[1] and Geva et al.[2] observe drift in dCA1 spatial representations while animals explore familiar, static environments. Long-term recording studies have recently shown that variability in animal behavior dramatically affects hippocampal representation.[8] Indeed, Khatib et al.[1] and Geva et al.[2] performed rigorous control analyses to demonstrate that variation along several behavioral axes did not explain their experience-dependent effects on representational drift per se (see the papers' supplemental information[1,2]). However, active experience is inextricably linked to the accumulation of behavioral variation—to be active *is* to vary one's behavior. From a perhaps subtle but different perspective, we could view these findings[1,2] to be consistent with the view that behavioral variability is a determinant of drift.[8] However, to our knowledge, no experiments have systematically addressed how variability of the *environment* affects representational drift, wherein systematic comparisons can be made across static versus variable (but recurring) contexts. It is possible that variability of the environment could either increase or paradoxically decrease representational drift. On the one hand, we imagine environmental variation might increase drift because of variability in behavior and experience while, on the other hand, variation of environment could decrease drift (i.e., increase stability) because of new demand to discriminate between variants of experience. Future experiments should therefore attempt to dissociate the impact of environmental and behavioral variability on long-term representation and whether these sources of variation have similar or opposing effects.

While Khatib et al.[1] and Geva et al.[2] illustrate the effect of active "online" experience on representational drift, the impact of "offline" dynamics (e.g., during sleep) on representational drift is not well understood. Decades of research have demonstrated that sequences of neural activity and their representational structure from awake episodes are reactivated, or "replayed," during sharp-wave ripples (SWRs) in restful and sleeping states,[9] and growing evidence suggests that such events have an important role in memory-guided behavior. A recent study showed that replay during SWRs predicts the long-term stability of spatial mapping in the hippocampus.[9] While the relationship between active experience versus replay and representational drift remains to be disentangled, we speculate that each could have distinct, possibly opposing effects on drift.

Finally, the impact of representational drift on animal and human cognition remains an exciting yet unexplored research direction. While the hippocampus has a well-described and central role in episodic memory, it remains unclear how representational drift relates to such cognitive functions. The encoding specificity hypothesis suggests that memory requires the reactivation of a distributed pattern of activity present during prior learning.[10] However, the drift phenomenon challenges this intuition and tasks us to reconsider how neural representation directs mnemonic behavior. Perhaps the organization of neural representations, rather than the tuning of individual neurons, is the determinant of memory-guided behavior.[1,2,5–7] Future experiments should examine how learning impacts the organization of neural representations across protracted experience and whether representational drift or organization have similar or dissociable behavioral consequences.

The studies from Khatib et al.[1] and Geva et al.[2] echo a fundamental theme reverberating throughout systems neuroscience—namely, that our brains' representation of the world hangs in balance between stability and plasticity. This delicate dance manifests in various aspects

of neural representation and cognition—from learning and adaptation to disease and recovery. These compelling and complementary studies from Khatib et al. and Geva et al. reinforce that representational drift is a meaningful, experience-dependent process and open new doors for future research programs to elucidate this complex and diverse phenomenon. Specifically, we set our sights toward experiments that seek to understand how plasticity mechanisms, variability in behavior and environments, learning, and remembering cause the brain's representations of our dynamic world to evolve.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Timing matters: A protective role of astrocyte reactivity in neurodegeneration

Daniela Rojo[1] and Erin M. Gibson[1,*]
[1]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, CA 94305, USA
*Correspondence: egibson1@stanford.edu
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Sheehan and Nadarajah et al.[1] identified that *Bmal1* loss from astrocytes induces the expression of BAG3, a macroautophagy chaperone enriched in Alzheimer's disease patients and in disease-associated astrocytes, enhancing the phagocytosis of misfolded proteins and preventing tau and alpha-synuclein pathologies.

Alzheimer's disease (AD) and Parkinson's disease (PD) are progressive neurodegenerative disorders that affect the central nervous system and currently have no cure.[2] Even though these diseases have distinct clinical features, leading to cognitive or motor decline, they both involve the misfolding and aggregation of proteins like β-amyloid, tau, or αSynuclein (αSyn).[2] Hence, understanding the mechanisms of proteome homeostasis is imperative for minimizing misfolded protein aggregates and reducing or reverting symptomatology for both AD and PD.

Increasing evidence suggests that tau and αSyn pathologies are associated with pronounced microglial and astrocyte activation.[3] But whether astrocyte activation is protective or deleterious for the progression of pathologies associated with AD or PD is still under debate. While decreasing astrocyte reactivity through α2-Na^+/K^+ ATPase inhibition has been shown to be protective for tauopathy development,[4] recent evidence suggests that astrocyte reactivity also has a protective effect by inducing proteostasis through the JAK2-STAT3 axis.[5] One particular mechanism shown to control cell-autonomous astrocyte reactivity is the circadian molecular transcription factor BMAL1.[6] Sleep and circadian disruptions are common in both AD and PD and can precede the onset of the disease.[7] BMAL1 acts as a transcriptional regulator of astrocytes and its disruption leads to a distinct astrogliosis signature through a glutathione-dependent response.[6] Whether the characteristic astrocyte reactivity induced by BMAL1 deletion is protective or deleterious for the progression of neurodegenerative