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Utility of the Idling Brain: Abstraction of New Knowledge

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Using clever experimental design and exploiting the high temporal resolution power of magnetoencephalography, Liu et al. show in humans how "offline" reactivation of brain patterns allows the abstraction of new knowledge from previous experience. The key mechanism may involve hippocampal sharp-wave ripples.

Creative people claim that their best ideas come not when they focus hard on a given problem and potential solutions but when their brain is idling (Andreasen, 2011). Who is doing the work in the idling, subconscious brain? One option is Descartes' imagined "little man" (*homunculus*). A more contemporary hypothesis is that hippocampal sharp-wave ripples (SPW-Rs) are in charge. In this issue of *Cell*, Liu et al., (2019) give credibility to the latter idea.

SPW-Rs in the hippocampus are considered a key mechanism for memory consolidation and action planning. SPW-Rs are found in every mammal investigated to date in the same form and shape (110–200 Hz oscillations) and may serve identical functions. While both inhibition and excitation increase during SPW-Rs, the overall result is a several-fold excitatory gain, making SPW-Rs especially suitable to engage wide areas of the neocortex and subcortical targets. SPW-Rs are initiated by the extensive recurrent axons of the CA2-3 pyramidal cells of the idling brain when subcortical neurotransmitters reduce their grip on hippocampal networks.

Temporal ordering of neurons during SPW-Rs often reflects task-related firing patterns—for example, sequential activity of place cells as a rodent traverses through the different corridors of the maze. Within a single SPW-R event, snippets or, occasionally, long segments of task-related sequential firing, are "replayed." This compressed replay is like the scaled version of a song or speech. But SPW-Rs can also play palindrome, unfolding the same sequence either forward or backward. Extensive research has revealed that the spike content of SPW-R is not a truthful replay of the experienced past. Instead, recent experience is embedded into a preformed backbone of network dynamics and guided by the brain's existing knowledge base. Thus, spontaneous replay of sequences reflects the brain's "beliefs" more than reproduces the true structure of world events, weaving together paths and events that have never been directly experienced and thereby facilitating creative thoughts and planning. In summary, SPW-Rs reflect a putative mechanism for inference and abstraction guided by the goals and interests of the brain (Buzsáki, 2015; Foster, 2017; Joo and Frank, 2018). These fascinating speculations emerged largely from experiments on rodents performing spatial tasks. Now enters the story by Liu et al., executed on human subjects.

Liu et al. asked whether abstract knowledge guides replay of new experiences. The short answer is yes. To address their goals, they designed experiments in which rules or schemas were inferred from visually experienced series of pictures. The first experiment followed the classical design of transitive inference (Figure 1). On day 1, the subjects were shown a scrambled sequence of picture pairs from which they could figure out the true order of two sequences. On day 2, they were presented new picture pairs in a scrambled order that adhered to the same rule learned on day 1 (the authors refer to this stage as "applied learning"). In the final stage, a picture of one sequence was associated with monetary reward, while another remained neutral ("value learning"). Before and after the value-learning phase, the subjects had resting periods of 5 min each. To monitor brain activity, the researchers recorded whole-brain magnetoencephalography (MEG) signals from the participants.

Liu et al., were able to decode each picture from patterns of MEG sensor activity ("stimulus code") and searched for their spontaneous reoccurrence in the MEG patterns during the 5-min "brain idling" epochs. Importantly, they found that spontaneous reactivation patterns typically conformed to the rule-defined sequence and not the presented and visually experienced order (Figure 1). These sequences were temporally compressed, similar to SPW-R replay in rodents. Furthermore, while the first resting epoch sequences were dominantly in a forward direction, following the value-learning phase, sequences reversed their order, reminiscent of the reversed replay sequences of hippocampal place cells after large rewards in rodents (Ambrose et al., 2016).

To rule out that spontaneous replay was a result of multiple associations rather than true inference, Liu et al. designed a second experiment, in which the subjects were explicitly told about the order rule on day 1 followed by presentation of novel pictures and their rule-based classification on day 2. As in the first experiment, they found evidence for forward sequences of rule-defined transitions rather than sequences of the experienced order of the pictures. Thus, these findings reinforce the interpretation that reordering of the experienced pictures was guided by the acquired rule.

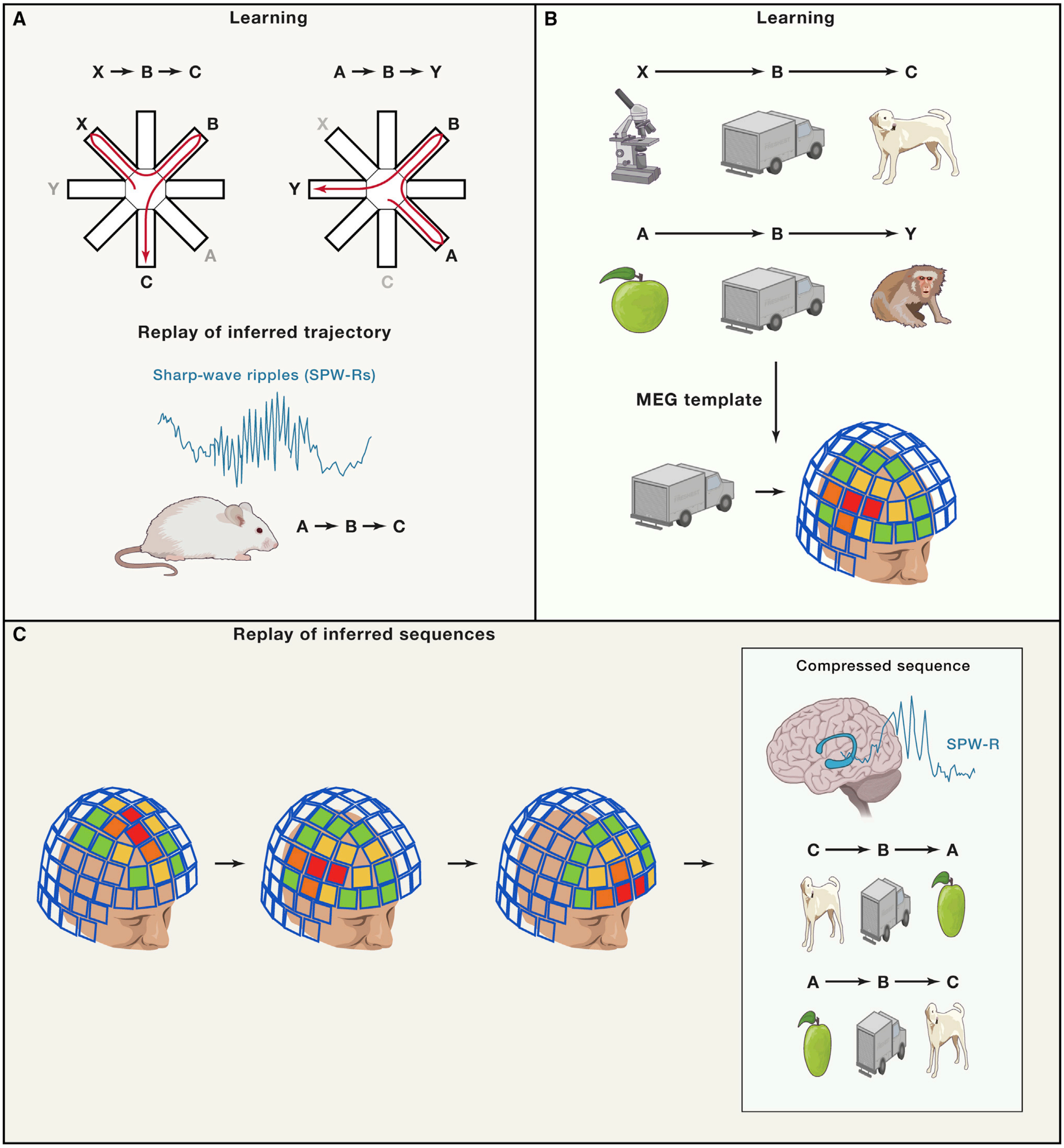

Figure 1. SPW-Rs May Assist with the Emergence of Abstract Knowledge

(A) Inference of an efficient novel path in rodents. In the learning phase, the rat is forced to follow either X-B-C or A-B-Y paths (above). During rest, compressed versions of the taken trajectories (i.e., place cell sequences), as well as not experienced paths are replayed and mixed in a compressed manner during SPW-Rs. This process allows the animal to infer a new path (A-B-C) based on transition rule between reward locations previously learned.

(B) Rule-based ordering of events. Subjects learn the rule from experiencing scrambled fragments. MEG is used to identify correlates of each presented set of pictures (“stimulus coding”).

(C) During rest periods, spontaneous occurrence of the picture correlates in the MEG were identified. Liu et al. demonstrate that the time-compressed replay sequence of the pictures follows the order of the acquired rule (forward or reverse when the items are rewarded) rather than the order of their physical appearances during the learning phase. The emergence of picture correlates were consistently preceded by rule-coding events, associated with ripple-band power increase (100–160 Hz), in a subset of MEG sensors, potentially corresponding to the occurrence of hippocampal SPW-Rs.

They also provide mechanistic insights showing that the replay of the position of a picture in the inferred sequence ("position code") consistently led replay of picture identity with a 50-ms lag, suggesting that the learned rule was critical for retrieving the correct item for the current place in a sequence. Thus, subconscious replay does not simply stitch together experienced non-spatial events but can construct entirely novel sequences determined by acquired or existing abstract rules.

Do hippocampal SPW-Rs contribute rule-guided replay? If so, one expects a power increase at 100–180 Hz at moments with high probability of spontaneous reactivations of MEG signals. This is exactly what the authors found in both experiments. They went even further and showed that the constellation of sensors with increased ripple-band power was similar to sensors that helped source localize hippocampal signals in a previous study (Dalal et al., 2013). These findings support the idea that SPW-Rs are part of a brain mechanism leading to abstraction of new concepts.

As is the case with any major discovery, the present observations invite criticism as well. Ripples also emerge in neocortical structures and often coincide with hippocampal SPW-Rs (Vaz et al., 2019). Therefore, further rigorous work is needed to establish that the ripple-power increase reported in the Liu et al. paper is in fact related to hippocampal replay. One would also like to know to what extent the preexisting brain dynamic affects the order of replay (Dragoi and Tonegawa, 2011; Buzsaki 2019). Finally, what is the relationship between the abstracted high-order constellations of MEG signals and spiking neuronal assemblies in both hippocampus and neocortex? Nevertheless, the work by Liu et al. opens up new opportunities to investigate hippocampal-neocortical interactions. Detection of SPW-Rs in human subjects can be combined with non-invasive stimulation methods to couple SPW-Rs to neocortical events, which may lead to novel approaches to improve cognitive performance in both normal subjects and disease. Overall, we learned that brain idling is useful.

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Counting the Cuts: MAZTER-Seq Quantifies m^{6}A Levels Using a Methylation-Sensitive Ribonuclease

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Garcia-Campos et al. describe MAZTER-seq, which deploys a sequence-specific, methylation-sensitive bacterial single-stranded ribonuclease MazF to provide nucleotide-resolution quantification of m^{6}A methylation sites. The study reveals many new sites and supports the idea of a predictable "m^{6}A code," where methylation levels are dictated primarily by local sequence at the site of methylation.

RNA modifications form a new layer of gene expression regulation in organisms ranging from yeast to human and plants. Of these, N^6-methyladenosine (m^{6}A) is the most abundant internal RNA modification found on messenger RNAs (mRNAs). Discovered almost 50 years ago, the m^{6}A mark sprang back into research focus with the ability to globally profile the marks on RNAs using an antibody-based approach (Dominissini et al., 2012; Meyer et al., 2012). Recognition of