11). The study of Okobi *et al.* is in accordance with these findings, because cooling of the respective motor cortical region increases the number of notes but not note duration, indicating that vocal pattern production is further downstream in the neural network. By contrast, cooling of the human motor cortex also leads to severe deterioration of the pattern of speech signals, which are directly produced by motor cortex (*12*). Future studies should elucidate at which brainstem level the motor cortex is capable of precisely timing vocal output in these mice.

Recent studies in house mice observed a direct connection from the motor cortex to the ventrolateral brainstem (*13*), a crucial structure in the primary vocal motor network (*1*, *4*). Okobi *et al.* reported short response latencies of vocal muscles after electrical stimulation of the motor cortex, suggesting a direct connection to a lower brainstem level. However, direct motor control via the periaqueductal gray (PAG) of the midbrain, another crucial structure within the primary vocal motor network, is plausible as well, especially because preliminary data suggest that the PAG shapes vocal production in rodents (*14*).

Additionally, it is important to decipher the interconnection of the motor cortex with auditory cortical structures in these mice, enabling the observed rapid and precise vocal timing. The auditory cortex in marmoset monkeys mediates rapid and precisely timed audio-vocal behavior (*15*), another crucial pre-adaptation for the evolution of complex learned audio-vocal integration systems. It will be interesting to see whether and how direct interactions between auditory and motor cortical areas underlie the observed audio-vocal behavior in rodents as well. For these questions, the Alston's singing mouse adds a new model system to investigate cortical control mechanisms underlying vocal communication systems in mammals. ■

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NEUROSCIENCE

Ripples for memory retrieval in humans

Neural activity synchronizes between brain regions when memory is recalled

By **Jennifer Gelinas**

How do we remember our experiences? The mental skill of bringing previously encountered people, events, and objects to mind is intuitive, but how neural circuits enable this episodic memory retrieval remains a fundamental question in neuroscience. On page 975 of this issue, Vaz *et al.* (*1*) use intracranial electrophysiological recordings in humans to identify a putative mechanism involved in memory retrieval: synchronized occurrence of high-frequency oscillations across brain regions. Their findings highlight the importance of dynamic interactions between brain areas in mediating complex cognitive processes and suggest a biomarker for pinpointing neural populations involved in different memories.

Early studies of patients with neurologic diseases such as epilepsy established that the medial temporal lobe (MTL) is critical for episodic memory (*2*), but this brain region does not operate in isolation. Structural brain connectivity reveals that the MTL has dense reciprocal connections with association cortices (areas that perform multimodal, advanced information processing), which in turn communicate with the primary cortices (areas that receive sensory signals, such as sounds, from the environment) (*3*). The position of the MTL at the apex of this pyramid of information flow enables it to integrate multimodal sensory information in space and time, setting the stage for episodic memory encoding and retrieval. Therefore, the search for neural signatures of this memory type focuses on interactions between the MTL and connected structures. Vaz *et al.* were able to simultaneously investigate the neural activity occurring in these brain regions by analyzing data from patients undergoing electrophysiological mapping as part of a clinical work-up for epilepsy surgery.

How can such interactions between brain structures be identified? Activity in neural populations often takes the form of oscillations that can parse individual neurons' action potentials into precisely timed chunks suitable for transmission to connected populations (*4*). Furthermore, when separate brain regions jointly engage in oscillatory activity, intercortical communication is facilitated because action potentials can arrive during a period of heightened neuronal excitability, increasing the likelihood that the incoming signal will engage local neural networks in relevant processing (*5*). Periods of oscillatory coupling between brain regions can thereby establish preferential communication channels during discrete epochs in time.

Ripples are high-frequency (110 to 200 Hz) oscillations initially characterized in the rodent hippocampus that are extensively implicated in transmitting information within memory networks (*6*). These short (40 to 100 ms) oscillations are the most highly synchronized physiological events in the brain, inducing robust increases in neural excitability locally and within connected brain regions (*7*). Most importantly, studies in rodents demonstrated that activity of individual neurons (neural spiking) during ripples is highly organized and can represent a temporally compressed version of neural activity patterns that occur during previous waking experiences (*8*). Hippocampal ripples can also induce reactivation of neural spiking patterns in downstream targets, such as the medial prefrontal cortex (*9*) and posterior parietal cortex (*10*). Because ripples occur frequently during waking immobility and non–rapid eye movement (NREM) sleep, they are posited to facilitate information transfer between hippocampal and neocortical networks by replaying waking neural activity during offline states (*11*).

Numerous experimental observations have expanded the diversity of ripples beyond the hippocampus, including ripples that occur in humans (*12*, *13*) and in rodent association cortices (*14*). Vaz *et al.* contribute to these findings by characterizing ripples in the human MTL, as well as in association and primary cortices. What is the relationship, if any, between ripples that occur in these different

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brain regions, and how does their existence inform our understanding of neural networks involved in memory? In rodents, the occurrence of ripples in the hippocampus and association cortex is correlated (*14*). Similarly, Vaz *et al.* found that ripples in the MTL were significantly coupled to ripples in the temporal association cortex (a region involved in language and multisensory integration), but not primary cortices. These results suggest that dynamic high-frequency oscillatory coupling may establish specific time windows for preferential communication between the MTL and association cortices, enabling these brain regions to effectively cooperate in information processing.

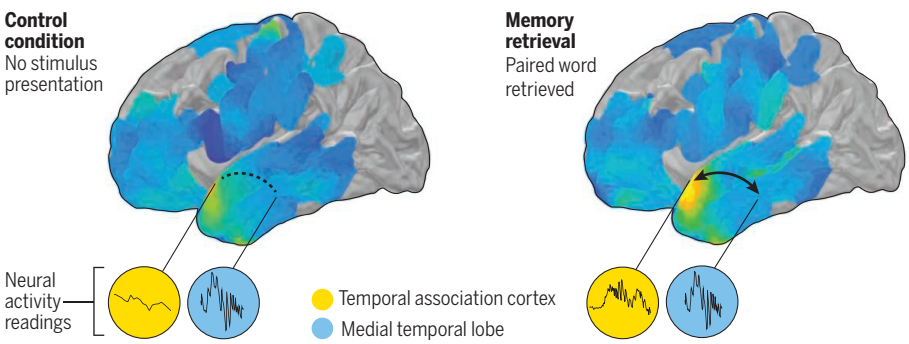
Vaz *et al.* establish the functional importance of this interregional ripple coupling during a memory task wherein human participants recall new associations between pairs of words. They find that both the occurrence rate and degree of MTL–temporal association cortex ripple coupling increase selectively during trials with successful memory performance. These effects were not observed in other association cortices (such as prefrontal or parietal cortices), which were presumably not required for the performance of this language-based task. The demonstration that ripple coupling between the MTL and different association cortices can be driven by varying task requirements would further strengthen the mechanistic interpretation of this phenomenon.

The study of Vaz *et al.* with human participants also permits key insight into the neural mechanisms specifically involved in memory retrieval (accessing a previously stored memory), rather than memory consolidation (strengthening a memory for long-term storage), which has been well studied in animal models (*15*). The memory task employed by Vaz *et al.* involved acquiring a timed verbal response or a pass on any given trial. They found that increases in ripple occurrence and coupling occurred during successful memory retrieval, but not during pass or incorrect trials or during encoding (when the memory is first established). Coupled ripples were also associated with a reinstatement of cortical activity patterns that were present during encoding of the word pair to be remembered, offering the possibility that the ripples may "prime" the network for the subsequent conscious process of recollection in this task.

Coupled ripples may serve as a biomarker for the "when" and "where" of memory retrieval in the brain, but the neural spiking sequences embedded in their oscillatory cycles define "what" is being retrieved (see the figure). Further investigation into these neural signals will help us to understand the syntax (*4*) that forms the basis of our experiential memories, and perhaps lay the foundation for interventions aimed at improving memory function. ■

Biomarker for memory retrieval

Ripples are synchronized between the medial temporal lobe and temporal association cortex during successful memory retrieval, but not during baseline conditions.



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GEOLOGY

How high were these mountains?

An iterative approach is needed to constrain the past elevation of mountain belts

By **Douwe J. J. van Hinsbergen** *and* **Lydian M. Boschman**

Paleoaltimetry—the quantitative estimate of the past elevation of land surfaces such as mountain belts—is notoriously difficult to constrain. To estimate past elevation, geologists study sedimentary rocks that accumulated in freshwater lakes in ancient mountain belts. They compare fossils or oxygen stable isotopes (the ratio of which is elevation-dependent) from these rocks with present-day records from elevated areas (*1*). One region where paleoaltimetry studies are widely conducted is the Tibetan Plateau, which owes its extreme elevation to intense deformation that started at least 70 million years ago during subduction of the Indian plate below Asia. However, elevation estimates for the region—for example, for the Eocene (~40 million years ago)—based on either fossils or stable isotopes differ by kilometers (*2*, *3*). On page 946 of this issue, Botsyun *et al.* (*4*) provide an explanation for this discrepancy and bring the two types of estimate nearer to agreement.

The authors used a numerical model that couples stable isotopes with atmospheric circulation (*5*). They show that changes in past atmospheric circulation can dramatically affect the relationship between oxygen isotope ratios and elevation. Using their circulation model, they recalibrated the oxygen-isotope paleoaltimeter for Eocene Tibet, using a set of paleogeographic scenarios as input, and brought the isotope-based estimates of Eocene Tibetan elevation down by several kilometers to arguably within the range of fossil-based estimates. This result implies that much of the surface elevation of the Tibetan Plateau was acquired after much of the crustal deformation took place, suggesting that processes in the underlying mantle may have played a key role in the uplift.

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Ripples for memory retrieval in humans

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