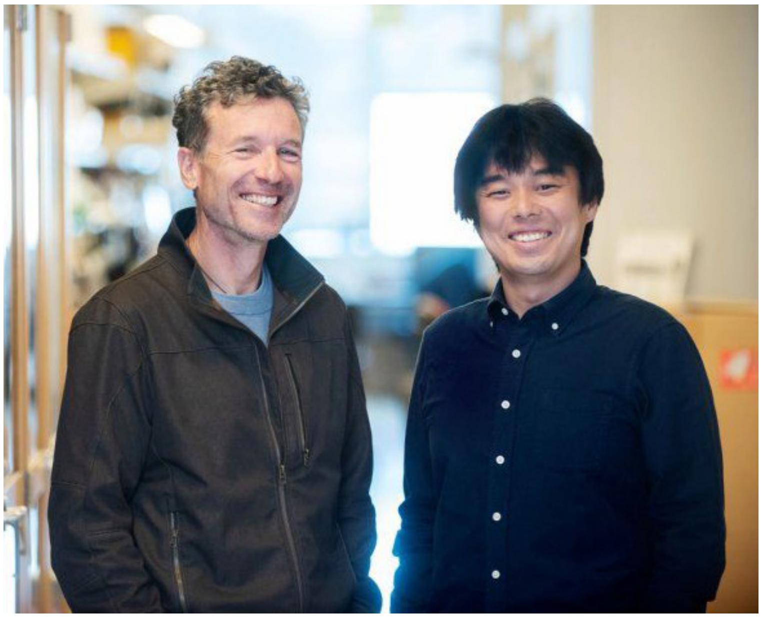
REM'S WINDOW INTO THE DREAM WORLD



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Dr. Massimo Scanziani, Ph.D., *is a professor of physiology at the University of California, San Francisco, and has been a Howard Hughes Medical Institute Investigator since 2008. Dr. Scanziani received his Ph.D. in neurophysiology at the University of Zurich and the Swiss Federal Institute of Technology. His research focuses on understanding the structure and function of neural circuits in the mammalian brain. His studies span from in vitro investigation of neurons to in vivo analysis of live animals as they process sensory information.*

Dr. Yuta Senzai, Ph.D., *is a postdoctoral scholar in the Scanziani Lab. After his undergraduate studies in Japan, Dr. Senzai completed his Ph.D. at New York University. He studies sensory and navigation systems during wakefulness and sleep in mouse brains to understand perception and the role of sleep in learning and memory.*

In this interview, we were honored to speak with both Scanziani and Senzai about the complex ways our brain works while we sleep, dream, and experience the world around us.

BSJ: Could you both describe your individual journeys that brought you into studying neurophysiology and vision at UCSF?

MS: I was trained as a synaptic physiologist. I completed my graduate studies in Switzerland and then did my postdoctorate here at UCSF. At the time, my interest was in investigating what happens at the synapse, right at the contact point between two neurons. After my postdoctoral studies at UCSF, I returned to Europe in the late '90s and started my own lab. I then realized that it was no longer the role of neurophysiologists to describe the function of synapses. Instead, this topic was now more pertinent to molecular biologists as they were making significant advancements in understanding the fundamental role of proteins in generating communication between neurons. Despite my interest in synapses, I was just starting my independent career and could not shift my physiology-focused lab to one of molecular biology. Instead, I thought about the open problems that I could address using the skills I had learned so far, namely by measuring electrical signals in nervous tissue. Rather than studying a single synapse, I decided to observe the communication taking place in circuits of excitatory and inhibitory neurons. Despite the successes obtained by my lab in Switzerland, I yearned to go back to California; I thought of it as a place "where things happen." I got an offer at the University of California, San Diego, and moved my lab there 20 years ago. In San Diego, my research on the circuits of neurons flourished, but my feelings of malaise eventually returned. I was studying those circuits in brain slices kept alive in petri dishes; however, I longed to study how these neural circuits function in an intact brain. I wanted to see them perform under conditions that are more similar to those within which they operate naturally. I decided to focus on the visual system because its parameter space had been studied incredibly well for the past 60 years starting with the work of David Hubel and Torsten Wiesel. Following this previous scientific research, we knew exactly what type of visual stimulus to give an animal in order to record signals from the precise parts that process visual information. A professor at UCSF, Dr. Stryker, had discovered that the responses to visual stimuli recorded in the brains of cats and monkeys could be perfectly reproduced in that of mice. Thus, I chose to study neuronal circuits in the visual system of mice, a simpler model system than a cat or a primate. It has been absolutely fascinating to discover the specificity of the responses of neuronal circuits to visual stimuli and it has been the focus of my research for the past 15 years. That was my journey–from synapses to circuits to vision.

YS: As a medical student in Japan, I developed an interest in the brain's ability to generate activity and representation that supports our cognitive processes, like perception. I decided to pursue this interest during my Ph.D. at NYU by studying the hippocampus. The nice thing about the hippocampus research is that the spontaneous activity internally generated during non-REM sleep can represent a replay of what is experienced during wakefulness. I then decided to pursue my postdoctoral studies with Dr. Scanziani, focusing on the generative aspect of the brain that supports our visual perception. This eventually led me to study perception during REM sleep.

BSJ: In your recent report in *Science*, you discuss how Rapid Eye Movement (REM) can be a response to dreams. How would you define a dream?

MS: One of the broadest possible ways to define a dream is as the purest expression of our internal model of the world. In a dream, we are secluded from the environment as our senses are completely internalized. Despite the fact that we are actively removing ourselves from our environment, we are able to generate a world within ourselves. This inward world is populated by the people and landscapes we know, as well as those created by us that are inspired by the real world. What is absolutely fascinating about dreams is that they are almost completely undisturbed by what is going on in the external world.

YS: In a way, dreams capture what you experience during wakefulness. You see familiar things or people you saw on a walk you took yesterday, or even ten years ago. On the other hand, dreams also capture a bit of weirdness. They have unusual aspects separate from our real-world experiences. To me, the important aspects of dreams are those that deviate from reality and capture our subconscious peculiarity.

BSJ: In both this recent report and previous projects, you use saccades as a way to measure and uncover more knowledge about how vision works. What are saccades, and why are they so useful in your research?

MS: Saccades are quick eye movements that humans perform during wakefulness. For instance, we perform saccades when we scan our environment by rapidly moving our eyes from one fixed visual point to another. We move our eyes in this way several times per second, mostly without even noticing. Every time we do this movement, the visual scene that is projected onto our eyes shifts several degrees, yet we are completely unaware of this process. From our perspective, the world is completely stable, despite the fact that the image that is projected from the world onto our retina moves two to three times per second. You can experiment with this phenomenon by tapping delicately on the corner of your eye. In this case, the image shifts on your retina in a way that is not initiated by you but instead by an external force for which the brain cannot account. And accordingly, you experience the movement of the visual image. This demonstrates how unstable our perception of the world would be if it was not for our brain's ability to censor it. Interestingly, what we learn from studying saccades is widely applicable to the human experience. When we move about the world, our brain automatically discounts the somatosensory stimuli we produce. Thus, your brain is constantly filtering out your self-generated stimuli, like the feeling of your toes touching the insides of your shoes or your sweater against your skin as you gesticulate in conversation, in order to be more responsive when receiving important external sensory information, like a tap on your shoulder.

This phenomenon also fascinated Dr. Satoru Miura, a Japanese postdoctoral researcher who led his own independent research in my lab. Dr. Miura discovered that the visual cortex treats a moving visual scene as a result of a moving environment differently from a moving visual scene as a consequence of saccadic movements. Despite this, the visual scene moves on the retina in the same way. In relation to our research on REM sleep, mice conduct saccades differently from humans. While humans are always exhibiting saccades while aware and awake, mice only perform saccades when they turn their heads as part of an orienting behavior. Essentially, saccades in mice are indicative of a change in heading. Knowing this, Dr. Yuta Senzai studied whether rapid eye movements occurring during REM sleep may indicate "virtual" changes in heading in the dreaming mouse.

BSJ: Rapid eye movements during REM sleep have been hypothesized to relate to the content of the ongoing dream for over fifty years, but verification of this proposal has proven difficult and yielded contradictory results. Could you explain the Head Direction (HD) system of a mouse and how you used this system to objectively prove this hypothesis?

YS: The HD system is a group of cells that exists in many parts of the brain and dictates where you look. Head direction is correlated to different neurons depending on the way the head turns. During wakefulness, this sense of head direction is computed by integrating information about your head and body movement using vestibular signals or proprioception with visual input changes. A previous colleague of mine, Dr. Adrien Peyrache, who is now a professor at McGill, discovered that these HD cells have similar activities during REM sleep. They showed that populations of HD cells behave as if they are moving around during wakefulness even if the head is not moving. Based on those previous findings, we decided to use this HD system. Head direction and eye movement are very tightly coupled in not only rodents but also primates.

> *The hypothesis that rapid eye movements are correlated to a subject's gaze in their dream fell out of favor. However, our data brings it back as a very likely possibility because eye movements are clearly not random.*

MS: The hypothesis that during REM sleep, the subject—in this case, the human subject—is somehow actively looking at the scenario of a dream has been hypothesized since the discovery of REM sleep in the early 1950s. When scientists would wake up their subjects while they were moving their eyes, almost invariably the subjects would report a dream. A common hypothesis among scientists back in the '50s and early '60s, was that the subjects may be moving their eyes to look at the scene in the dream, the so called "scanning hypothesis." Proving this was very difficult. As a scientist, you would use a special apparatus to monitor the eye movements under the closed eye lids of the sleeping subject, note the direction of the eye movement and wake up the subject and say, "What were you dreaming about?" The subject may say, "There was something coming to the right and a car coming from the left." The scientists were trying to match the narrative of the dream with the eye movements recorded just before waking up the subject. In the beginning, those experiments seemed to say, "Well, look, actually, the subject said that there was a person coming to the left and their eyes were looking to the left just before." But, as scientists tried to be more scrupulous, this approach didn't hold. The hypothesis that rapid eye movements are correlated to a subject's gaze in their dream fell out of favor. However, our data brings it back as a very likely possibility because eye movements are clearly not random.

BSJ: Your research revealed two different types of eye movements, which you called "leading" and "follower" eye movements. How do these movements differ from each other, and how do they relate to the mechanisms behind wakeful eye movement?

YS: During REM sleep, rapid eye movements occur in bursts. "Leading" eye movements are the first ones in the burst of rapid eye movements, and the "follower" eye movements follow these leading eye movements. The direction of leading eye movements is the same as the direction of the corresponding virtual head turns occurring during REM sleep, while the followers move to the opposite direction of virtual head turns. These two types of rapid eye movements during REM sleep can be homologous to the two types of eye movements observed during wakefulness: namely, eye movements that shift the gaze and eye movements that stabilize the gaze. The gaze-shifting eye movement changes your gaze from one point to another in the visual field, such as going from the PC monitor in front of me to my dog on the bed. The gaze-stabilizing eye movement, for example, stabilizes your gaze when you are riding a bike and your head direction changes quickly. In both rodents and humans, these two types of eye movements are commonly observed during wakefulness. Our speculation is that these two types of eye movements could also be translated as leader and follower eye movements during REM sleep. Leader eye movements could be related to shifting gazes in "dreams," and followers may help stabilize the gaze fixation on the dream imagery.

MS: To conceptualize leading and follower eye movements, you could imagine keeping your head still and moving your eyes to look at something on your left. Now imagine you want to look at something a little further to the left, and then something further than that. Eventually, your eyes are going to reach the end of their mobility. The first eye movement is an orienting eye movement. The other one is centering. As Yuta mentioned, this orienting and then re-centering, orienting and then re-centering, is actually something that occurs when we are awake by alternating a gaze shift with an image stabilization movement.

BSJ: Based on your findings in mice, why do you think lifelong blind individuals have rapid eye movements during REM despite not reporting any visual experience in their virtual dream world?

MS: This is a very important question for which we do not have an answer. We can only speculate. The observation that lifelong blind individuals still have rapid eye movement was one of the major criticisms of the scanning hypothesis in the '60s. These individuals do not even know what the visual environment is since they have always been blind. What are they looking at? My speculation is that a lot of our actions in the world occur even before we can shape them in a way that is coordinated with the outside world. The best example is the babbling of a baby. In an adult, most vocalizations are to speak, curse, sing, etc. Yet, a baby that does not know how to speak still babbles a lot. It does work its motor system and receives auditory feedback, but the babbles are meaningless. It is clearly not speaking English or Italian or Japanese, right? It is babbling. That does not preclude the fact that once you know how to use your vocalization, you use them to communicate abstract concepts. One can use that same framework to explain a movement. Eventually, rapid eye movements, once we know what they are and how to control them, allow us to shift our gaze in the visual world. Blind people move their eyes sometimes, even during wakefulness, despite the fact that their eyes are useless

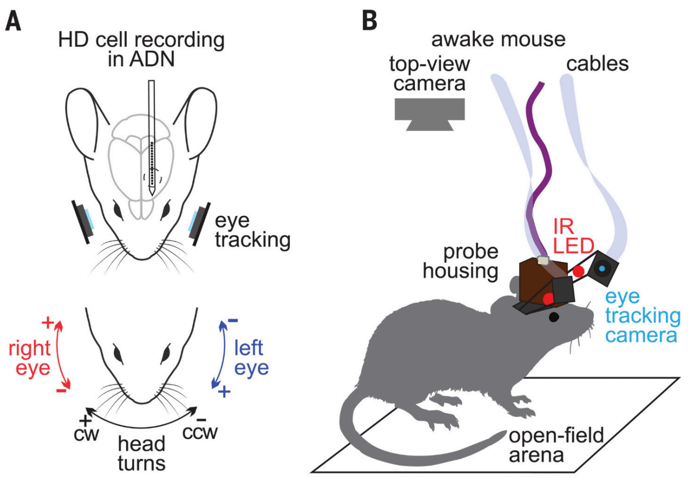

Figure 1: Extracellular linear probes (A) record head direction (HD) cells in the anterodorsal nucleus of the thalamus (ADN). *An eye-tracking camera (B) detects the heading of mice as they roam uninhibited during wakefulness.*[3]

to them. I suspect that what we are seeing during REM sleep, in people who have been lifelong blind and still move their eyes, is a little bit like the babbling of a baby who does not know how to speak.

YS: I think that when we move around in the environment, there are many other modalities besides vision that define the environment. My speculation is that blind people may be moving around in a dream not necessarily defined by vision. Since this orienting behavior is very conserved, blind individuals may still be able to move their eyes in conjunction with the orienting behavior because the two are tightly coupled. You can see those movements as a result of this orienting behavior in a dream.

MS: People must have looked at a lifelong blind person who hears a sound in a part of a room and moves, say, toward the sound. Do they also move their eyes in an orienting behavior toward the sound? That could be the type of orienting behavior of which Yuta is referring to. Your entire body moves towards a source of a stimulus, even if that stimulus is only heard or only touched. Blind people may also move their eyes toward a source of a stimulus when they turn their heads, even if their eyes are not involved.

BSJ: In one of your previous papers, you discuss the processes relating to distinguishing external motion from saccade-induced motion in the visual cortex. In the paper, you mention the connection between the thalamic pulvinar nucleus and the primary visual cortex. Could you elaborate on the role of the pulvinar, both in general and in sensory processing?

MS: The vast majority of the sensory input that we get is generated by ourselves, and a big part of our brain's work is to distinguish between what is self-generated and what is not self-generated. Our brain is very good at that. Imagine you come back home, alone at night when everything is dark. As you start walking, you can hear every step you make on the hard floor. Now imagine that suddenly, you hear the exact same sound but out of order with your actual steps. What do you do? You freak out! You hear exactly the same sound, but when it goes off a step, your brain immediately realizes you are not the source. Your brain continuously needs to take into account what is generated by you in order to be able to focus on what is not generated by you. This idea inspired this project.

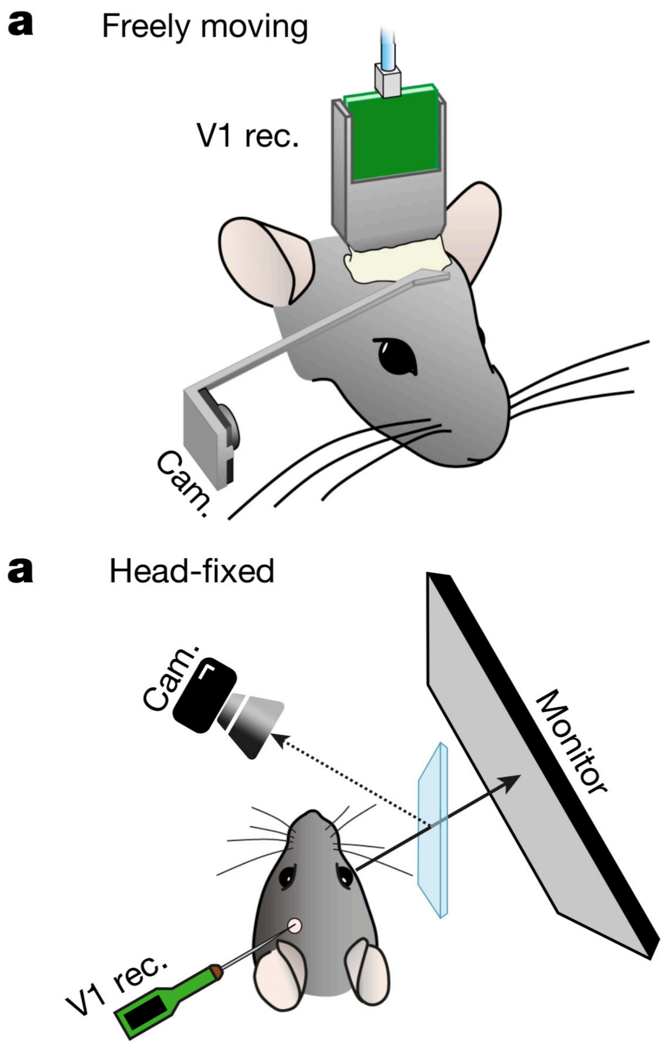

Figure 2: Mouse set-up when the head is freely moving versus fixed. *The mice move their head to change their line of sight. By fixing their head, it is possible to distinguish the external motion from saccades.*[2]

The pulvinar is one of the thalamic nuclei that has fascinated scores of scientists for decades. It has at least three roles in sensory processing. One important role of the pulvinar is to connect different areas of the cortex to one another. The cortex is divided into the primary visual cortex and then higher visual areas. Those areas are interconnected not only directly, but also very strongly indirectly through the pulvinar. The second role of the pulvinar is to transmit non-visual information to the visual cortex. For example, Satoru Miura discovered that the pulvinar identifies the self-generated motion of the visual scene and continuously sends the non-visual saccadic information to the visual cortex to say, "Hey, a saccade is about to happen. Oh, now it just happened." There are other types of non-visual signals that are transmitted from the pulvinar to the visual cortex. A postdoc in my lab, Dr. Guy Bouvier, has found that the vestibular system provides very important information for the visual cortex. The third role of the pulvinar, which has been known since the '60s, is that it sends visual information to the cortex from the superior colliculus. The superior colliculus, called "tectum" in all vertebrates but mammals, is a very important visual stage that receives direct input from the retina. What scientists have observed, and what my lab has also studied quite recently, is that the superior colliculus sends its own visual information to the cortex via the pulvinar. I am sure we are going to figure out many more roles as it is a very complex nucleus.

BSJ: Since REM sleep is essential to our neurological health, why do you think people often forget their dreams? Do you think that dreams we remember and dreams we do not remember serve different physiological purposes?

YS: We do not know exactly why some dreams are forgotten, so I can only speculate. Although many elements of REM sleep resemble wakefulness, noradrenaline, an important neuromodulator released during wakefulness to allow engagement to tasks, is completely gone during REM sleep. This kind of difference could make our dream experience more forgettable. We do not know the physiological functions of remembering a dream versus not. For example, people experiencing post-traumatic stress disorder, or PTSD, often report nightmares. Some people say that nightmares are protective or important for patients to heal. But, others say nightmares make their PTSD worse. In this case, the function of dreams, the dream experience, and how we remember dreams are not studied well. We hope that by studying brain activity during REM sleep in an animal model, we may gain a deeper understanding of these brain circuits in this basic mechanism.

BSJ: What are the biggest outstanding "black boxes" that exist in terms of understanding visual processes, and how do you plan to go about tackling them? Where do you draw inspiration for your research?

MS: I think the biggest black boxes to open up with regard to visual processing are the following. The first step of seeing is the result of the combination of two streams of information. One, the "bottom-up" stream, is what comes through our eyes—the actual information coming from the visual world. The other, the "top-down" stream, is our internal model of the world—what we know about the world. What we call seeing is the combination of what we see with our internal model of the world coupled with the actual sensory input. This combination triggers that perception: "Oh, I am seeing a face." The past 60–70 years of visual neuroscience have been extremely successful in figuring out the bottom-up stream, the mechanism by which the world enters our eyes. Our eyes transform visual stimuli into electrical signals, and those electrical signals are then elaborated by the brain to reveal specific properties of a visual scene like differences in luminance, edges, moving objects, etc. All of this bottom-up processing is very important, but it is not what we call seeing. Seeing is the combination of something that is bottom-up with something that is top-down, that is, with our internal model of the world; how this combination happens is, in my opinion, the next black box that will reveal some fundamental aspect of what we call seeing.

Part of where I draw inspiration for my research is introspection. It is from questions that come out of how I observe myself interacting with the world and other parties. I also find chance observations during experiments incredibly inspiring because they often are completely unexpected, and, because they are unexpected, if we make sense of them, then they might have a big explanatory power. But mostly, I am inspired by the creativity and smartness of the people that I am lucky to work with—wonderful younger scientists, like Yuta and Satoru Miura, come to work with me, and I get a lot of inspiration and insight from them.

YS: A similar question that I have is to understand how we visually perceive this world by comparing our knowledge of the external world versus our internal model. I think that REM sleep could be a good candidate because it seems that the external world has a very minimal impact during REM sleep. In a way, this detachment from the external world is kind of an ideal situation to understand how our brain creates perception or a representation of something in the brain. Understanding the world through this internal model is similar to the way research is conducted in other fields, like statistics or machine learning, or AI. I am still trying to get inspiration to put this idea into a more tangible system. Working off my own ideas and ideas that come from interacting with colleagues and a great mentor like Massimo allows me to come up with good hypotheses and experiments to test them.

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