Q&A: Memory, brain function, and behavior—exploring the intricate connection through fear memories

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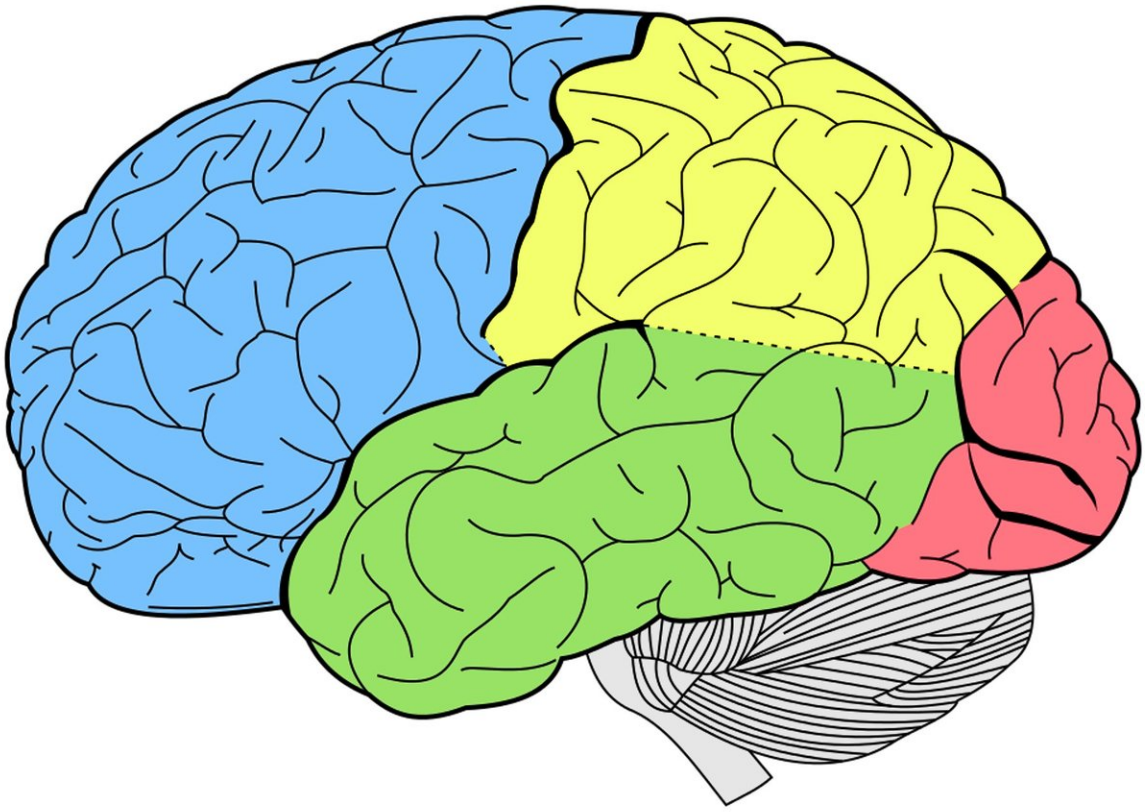

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In a world grappling with the complexities of mental health conditions

like anxiety, depression, and PTSD, new research from Boston University neuroscientist Dr. Steve Ramirez and collaborators offers a unique perspective.

The study, recently published in the *Journal of Neuroscience*, delves into the intricate relationship between fear memories, brain function, and behavioral responses.

Dr. Ramirez, along with his co-authors Kaitlyn Dorst, Ryan Senne, Anh Diep, Antje de Boer, Rebecca Suthard, Heloise Leblanc, Evan Ruesch, Sara Skelton, Olivia McKissick, and John Bladon, explore the elusive concept of fear engrams, shedding light on the physical manifestation of memory in the brain. As Ramirez emphasizes, the initiative was led by Dorst and Senne, with the project serving as the cornerstone of Dorst's Ph.D.

Beyond its implications for neuroscience, their research marks significant strides in understanding memory formation and holds promise for advancing our comprehension of various behavioral responses in different situations, with potential applications in the realm of mental health. In this Q&A, Dr. Ramirez discusses the motivations, challenges, and key findings of the study.

What motivated you and your research collaborators to study the influence of fear memories on behavior in different environments?

The first thing is that with fear memories, it's one of the most, if not the most, most studied kind of memory in rodents. It's something that gives us a quantitative, measurable behavioral readout.

So when an animal is in a fearful state, we can begin looking at how its

behavior has changed and mark those changes in behavior as like an index of fear. Fear memories in particular are our point because they lead to some stereotyped behaviors in animals such as freezing in place, which is one of many ways that fear manifests behaviorally in rodents..

So that's one angle. The second angle being that fear is such a core component of a variety of pathological states in the brain. So including probably especially PTSD, but also including generalized anxiety, for instance, and even certain components of depression for that matter.

So there's a very direct link between a fear memory and its capacity to evolve or devolve in a sense into a pathological state such as PTSD. It gives us a window into what's going on in those instances as well. We studied fear because we can measure it predictably in rodents, and it has direct translational relevance in disorders involving dysregulated fear responses as well.

Can you explain what fear engrams are and how you used optogenetics to reactivate them in the hippocampus?

An engram is this elusive term that generally means the physical manifestation of memory. So, whatever memory's physical identity is in the brain, that's what we term an engram. The overall architecture in the brain that supports the building that is memory. I say elusive because we don't really know what memory fully looks like in the brain. And we definitely don't know what an engram looks like.

But, we do have tips of the iceberg kind of hints that for the past decade, we've been able to really use a lot of cutting edge tools in neuroscience to study.

In our lab, we've made a lot of headway in visualizing the physical substrates of memories in the brain. For instance, we know that there are cells throughout the brain. It's a 3D phenomenon distributed throughout the brain but there are cells throughout the brain that are involved in the formation of a given memory such as a fear memory and that there are areas of the brain that are particularly active during the formation of a memory.

What were the main findings about freezing behavior in smaller versus larger environments during fear memory reactivation?

It's thankfully straightforward and science is often anything but. First, if we reactivate this fear memory when the animals are in a small environment, then they'll default to freezing–they stay in place. This is presumably an adaptive response so as to avoid detection by a potential threat. We think the brain has done the calculus of, can I escape this environment? Perhaps not. Let me sit in a corner and be vigilant and try to detect any potential threats. Thus, the behavior manifests as freezing.

The neat part is that in that same animal, if we reactivate the exact same cells that led to freezing in the small environment, everything is the exact same: the cells that we're activating, the fear memory that it corresponds to, the works. But, if we do that in a large environment, then it all goes away. The animals don't freeze anymore. If anything, a different repertoire of behaviors emerge.

Basically, they start doing other things that is just not freezing, and that was the initial take home for us, was that they, when we reactivate the fear memory up, or artificially, when we do that in the small environment, they freeze, when we do that in the large environment, they don't freeze.

What was cool for us about that finding in particular was that it means that these fear memory cells are not hardwired to produce the same exact response every single time they're reactivated. At some point, the brain determines, "I'm recalling a fear memory and now I have to figure out what's the most adaptive response."

Were there any challenges or obstacles you encountered during the research process, and how did you overcome them?

There are a couple. The first is that the behavior, ironically enough, was reasonably straightforward for us to reproduce and to do again and again and again–so that we were convinced that there was some element of truth there. In the second half of the study, and the one that probably takes up the most space in the paper, was figuring out what in the brain is mediating this difference.

As we observed, the animals are freezing when we artificially activate a memory in a small environment, and they're not freezing in the large environment. But, we're activating the same cells. So, what is different about the animal's brain state? What is the animal's brain state when we're reactivating this memory in the small environment compared to the large environment? Clearly it's manifesting as totally opposite behaviors–freezing and lack thereof.

So, we wanted to find out what in the brain is happening in those two conditions that are different. That led us down a multi-year rabbit hole of trying to map out activity patterns in the entire brain, as a result of stimulating these memories in these different sized environments. We went through a whole mess of technologies where we looked at the brain–we can actually make the brain completely transparent–so that we can take fancy microscopes and image the brain in three dimensions.

Think of it as a cellular MRI for rodents. We created these brain-wide maps of what's responsive in the brain when we stimulate a memory. Then we asked ourselves, how does that map of the brain in the small environment compare to the map of the brain when we're activating the memory in the large environment?

In short, there are similarities and differences. That there are certain parts of the brain that are always active when we stimulate a memory, regardless of the environments that the animals are in. But, then there are other parts that are only active in the large environment or only active when we do the experiment in the small environment.

That's neat because that lets us know that those areas that are not in common between the two might be the ones that are actually important in mediating the brain's decision to either freeze or to not freeze. However, this process was challenging because it required a lot of technical prowess such as making brains transparent and imaging them in three dimensions down at the cellular level.

How might the insights from this research be applied or extended in the future, particularly in the context of understanding and treating fear-related disorders?

Context clearly matters. One relatable example is that two people might be experiencing the same level of anxiety, but the underlying reason for that anxiety might be wildly different across the two people. The ways that anxiety affects the people behaviorally may also be very different. One person might be pacing up and down the room, whereas the other one is just kind of sitting and lost in their own thoughts.

The same faculty of cognition can appear two very different ways, in how it's expressed. In this case, we think it's the same thing with fear

memories—how they're expressed will depend on what the animal is experiencing. Perhaps in people, how a given memory is expressed also is going to depend on the context, like the who's there, the what, where, why, and so on.

So that's one angle, but I think that the more direct relevance is that we've known for a decade that these cells in the hippocampus are enough to jumpstart a memory when we reactivate them. But then there's the question of, what happens if we reactivate them, and we change up more than just the environment size? If we activate a fear memory, but while an animal is with his rodent buddies in the cage, will that change how that fear memory manifests differently?

In that sense, we hope it gives more of a roadmap on what these experiments can look like, and really build off the idea that we can activate memories and chart out what's happening throughout the brain in three dimensions. We can use that to try to continue this scavenger hunt of finding targets in the brain for mitigating fear responses.

In terms of broader implications, how could the findings of this study contribute to our understanding of the relationship between memory, brain function, and behavioral responses in various situations?

The biggest take home is that the brain processes a lot of information before a memory is translated into action. I think that for me, one of the most important points is that a thought–and I'm using thought and memory here interchangeably–particularly one linked to a memory, will make us feel all sorts of things associated with that memory.

Again, it could be a positive memory, it could be a negative memory, and everything in between, but it doesn't have to appear the same way. I

think it's a really important point for people to understand, because it serves as a reminder that the process of turning thought into action varies across individuals and what they are experiencing in real time.

Let's say I was sitting in front of you right now. I could go through the most euphoric memories that I have and the dimmest darkest memories that I have—go through the whole spectrum of emotion from happiness, gleefulness and euphoria to somber, pensive, or sad, the works.

But, I could go through all of that without ever really batting an eye, and you would never really know that those are the thoughts that I'm having unless I somehow volunteer that information. But the other thing to consider would be, maybe there are subtle things happening underneath the hood here that we could pick up on. Maybe when I'm thinking about sad memories I slouch a little bit more, my pupils dilate, or I sweat a little bit more.

Whereas when I recall positive memories, maybe I kind of chipper up a bit, my posture is better, my pupils dilate another way, and my heart rate goes up.

There are other not so obvious metrics for reading out a memory that I think can be used. Ultimately, I hope that this research at least inspires people to dive a bit more deeply into what's really going on and learn how our memories are ultimately leading to an action. I want to understand the magic that's happening, and I hope that the study helped unpack a little bit of that magic.

More information: Kaitlyn E. Dorst et al, Hippocampal engrams generate variable behavioral responses and brain-wide network states, *The Journal of Neuroscience* (2023). DOI: 10.1523/JNEUROSCI.0340-23.2023

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