From Molecules to the Mind

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How fitting that memory was the topic of this year's presidential symposium, as APS looks back in celebration of its first 25 years. Fitting, too, because the theme echoed that of a symposium at the very first APS convention held in Arlington, Virginia, in 1989. The 2013 panel of speakers — much like their predecessors — toured the science of memories, from the cells that encode them to the brain areas that retrieve them to the social experiences that spark them in the first place.

Altogether, the talks examined "the psychological and behavioral processes associated with how we learn and remember everything from the simplest of behaviors to the most complex information possible," said APS President Joseph E. Steinmetz of Ohio State University.

Biologist Ted Abel of the University of Pennsylvania gave the audience of psychological scientists a thorough explanation of the molecular processes involved in the formation of long-term memories. In particular, he focused on the molecule called CREB and a protein that binds to CREB to regulate gene transcription — the so-called "CREB binding protein." Abel and colleagues found it to be a central player in how the brain maintains old recollections.

"It turns out that the CREB binding protein is a major switch in long-term memory storage," Abel said.

The secret to the CREB binding protein's role is its ability to modify histones, the proteins wrapped around DNA. Within the nucleus of each neuron there are about 60 million possible combinations of histone modifications, said Abel. In important life moments, biochemical changes occur, followed by changes in gene expression, and as a result the experience is locked into mind.

In one study, Abel's lab isolated one of the key functional domains of the CREB binding protein in mice. By altering that domain, they were able to produce deficits in long-term memories: the mice could recall fear in a 24-hour test, but not in a one-hour test.

Other work has concentrated on a gene called Nr4a2 that appears to be critical to memory enhancement.

"More broadly, what I've told you about is a sort of field that's begun to be called behavioral epigenetics," Abel said. "In a sense, this is the field where nurture meets nature — where our experience interacts with our DNA and our genes."

Michael Fanselow, a behavioral neuroscientist at the University of California, Los Angeles, advanced the discussion of memory formation beyond individual cells to whole brain regions. Fanselow studies fear memories in rats, and has demonstrated that the amygdala is the hub of fear, while the hippocampus

stores any association with context or place. When rats receive hippocampal lesions after a fearful event, they lose their contextual fear, but not their ability to fear in general.

“The hippocampus doesn’t care so much about fear — what the hippocampus cares about is, where am I?” Fanselow said.

The amygdala is vital to the retrieval of fearful memories. But Fanselow and colleagues have found that other brain regions — notably, two areas in the prefrontal cortex — can pick up the contextual slack for the hippocampus if necessary. Rats whose hippocampus was surgically damaged *before* they had a fearful experience, for instance, remained terrified by the place where those bad memories were made.

“It seems when you don’t have a hippocampus and you try to learn something about context, other brain regions can compensate,” Fanselow said.

Lab tests have identified these other regions as the prelimbic and infralimbic cortices. In studies, rats without any lesions show normal fear conditioning — they encode a bad memory, then retrieve it when they’re back in the same place — and those with pre-memory hippocampal lesions adjust to do the same. But when hippocampal lesions are combined with small lesions to the prelimbic and infralimbic areas, the animals show no fear renewal at all.

“It looks like these two prefrontal regions act in a coordinated fashion … allowing the animal to learn context fear in the absence of a hippocampus,” he said.

The discussion progressed into the human brain with a talk from APS President-elect Elizabeth A. Phelps of New York University. Phelps has studied various techniques for controlling fearful memories. One way to do this is through simple “extinction.” By repeatedly exposing a person to a fearful stimulus until the stimulus loses its frightful impact, the power of the memory diminishes until it’s entirely absent.

“You don’t eliminate the original fear memory,” said Phelps. “Rather, you create a new safe memory which then comes to compete for expression, to see which one’s going to win out.”

Another approach to changing fear memories is called “emotion regulation.” This method, which is the basis for cognitive-behavior therapy, attempts to get a person to reevaluate whatever stimulus or situation is associated with the fear. During trials, for instance, subjects who thought of something calm when they saw a color (e.g., blue = ocean) showed decreased arousal compared to controls when that color was paired with a shock.

“I often call it the ‘glass is half full’ effect,” said Phelps of emotion regulation, “because it gets at the idea that how you view a stimulus has an important role in the emotional response that stimulus elicits in you.”

Phelps's latest work explores whether the very nature of harsh memories can be altered to permanently render them less painful. This strategy is called "reconsolidation." The idea is to reactivate a bad memory, then extinguish it in an impressionable state so that it hardens — or reconsolidates — into something less powerful. Just like updating a computer file, you're updating the memory into something quite new.

"This suggests to us that extinction during reconsolidation may have led to re-encoding of the memory as safe," she said. "We think that, consequently, the fear memory no longer exists in original fearful form."

Famed memory scientist Elizabeth F. Loftus, a past president of APS, made a perfect capper to the panel since she'd also been at that symposium 25 years earlier. Over the years, Loftus's research has shown that memories are hardly cemented into place. On the contrary, they often change based on new information learned after the fact — an effect Loftus, at the University of California, Irvine, calls the "misinformation paradigm."

"You expose people to misinformation, and it impairs their ability to accurately remember what they saw," she said.

Loftus and collaborator Charles Morgan, at the Yale School of Medicine, tested this paradigm on a group of military personnel who'd gone through a rigorous survival school training. During the training, these soldiers were hooded, thrown into cells, and given an abusive interrogation — just as they could be if captured in war. One might expect this highly stressful experience to lodge itself firmly into memory, but as Loftus showed, that wasn't quite the case.

In one test, researchers showed the soldiers pictures of the interrogator who had supposedly abused them during survival training. In fact, the picture looked nothing like the actual interrogator, but still this piece of misinformation planted itself into the original memory. When the soldiers were shown a lineup of faces to identify the actual interrogator, 84 percent chose the phony picture.

"I've learned in 25 or more years of working on these problems that just because a memory is expressed with emotion, with detail, with confidence — it doesn't mean that it's true," Loftus said.

References

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