NEWS

Memory hub could underlie social, cognitive quirks of autism

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For most of us, telling a tale from our childhood is a simple, often spontaneous act. For people with autism, however, relating life experiences — whether from years ago or yesterday — can be a tall order.

Autism has an unusual effect on memory: It disrupts the recall of everyday events but often goes with an enhanced ability to hold onto facts. Many people with autism can master enormous amounts of detail about a chosen interest, be it the London transit system or the life of Georgia O'Keeffe.

These traits, among others, implicate the brain's main memory hub, the hippocampus, in the condition. Preliminary studies in animals suggest that disruptions to the hippocampus and its circuits could underlie some of the cognitive difficulties common among people with autism[1,2].

Some of these problems, such as trouble remembering social information, may stem from problems with memory per se. But others may relate to memory only indirectly.

"We're recognizing that the hippocampus is really critical to a lot of the things that are clearly absent in autism — things like being able to flexibly make decisions based on past experiences," says **Loren Frank**, professor of physiology at the University of California, San Francisco.

Studies of the hippocampus could one day help to explain features of autism ranging from poor social skills to difficulty switching from one idea to another — an aptitude known as 'cognitive flexibility,' Frank says.

This brain region might also lend clues to therapy: People with autism may be able to use some unusual cognitive strengths to compensate for their weaknesses.

Social scripts:

The hippocampus' name derives from its resemblance to a seahorse. In the 1950s, scientists established its role in memory after noting that people with a damaged hippocampus could not form new memories.

The anatomy of the structure may be somewhat atypical in the condition. One study of 8- to 12-year-olds found that children with autism have a larger right hippocampus than controls do, but this size difference diminishes as the children get older[3].

The consequences of this anatomical oddity are unclear. But research hints that there are specific strengths and weaknesses in the way people with autism remember and learn.[4]

The hippocampus governs declarative memory, the conscious recall of facts and events. People with autism struggle with one aspect of declarative memory — **autobiographical events**. A detailed memory such as eating caramel corn at a carnival in yellow rain boots doesn't stick in their minds[5].

On the other hand, they are good at, and may even excel at, retaining names, dates and definitions, and other facts. These skills also fall under the purview of declarative memory. In one 2008 study, a group of individuals with autism with average or above-average intelligence named the objects in a series of pictures at least as rapidly and accurately as controls[6].

In fact, declarative memory may help people with autism **make up for some of their other difficulties**, says **Michael Ullman**, professor of neuroscience at Georgetown University in Washington, D.C.[7]. Because they have trouble with social skills, they may memorize 'scripts' for, say, how to behave at a birthday party or what to say when meeting someone new.

Tongue-tied:

Although the hippocampus is often said to 'store' memories, it doesn't function like a filing cabinet, says Frank. Instead, it's more like an orchestra conductor, touching off patterns of activity elsewhere in the brain — in areas needed for processing sensory stimuli, emotions and so on — that result in the experience of a memory.

As a result, a glitch in the hippocampus, or its broader cognitive circuit, does not necessarily result in a memory storage problem. For example, people with autism may have trouble using memories to make decisions — a process that requires rapid toggling between internal thoughts and the external world. Deciding what to say in a conversation, for instance, involves listening to someone, registering their meaning and matching that with stored information and experiences — in milliseconds.

“Being able to switch attention back and forth is a critical aspect of our normal cognitive processes,” Frank says. “And that seems like something that may not be working well in autism.”

Frank and his colleagues have found that disrupting neural traffic between the hippocampus and areas of the cerebral cortex, the brain’s outer shell, in rats leads to autism-like **repetitive behaviors**[8]. These animals may resort to such repetition because they cannot flexibly respond to varied, unpredictable stimuli, Frank says.

Frank’s team is studying a rat model of **fragile X syndrome**, a genetic condition related to autism, to see whether the rats have abnormalities in hippocampal circuits.

Conflict resolution:

People with autism may also have trouble altering memories in the face of conflicting information. For example, boys with fragile X syndrome are just as good as controls are at remembering items on a list. But they struggle with tasks that require integrating knowledge from different sources.[9] “They tend to have a deficit when they’re asked to do something that contradicts what they were initially asked to do,” says **Andre Fenton**, professor of neural science at New York University.

Fenton and his team are investigating these ideas in a mouse model of fragile X syndrome. They have found that fragile X mice can learn to avoid an area that delivers an electric shock. But when the shock zone moves, they are slow to learn its new location[2].

The team has identified one unusual feature in the mice, in hippocampus cells that track an animal’s location in space: The firing patterns of the cells are highly similar, even in different conditions. “It’s almost like it’s hyper-perfect. It’s hyper-reliable,” Fenton says. These over-synchronized neural signatures may underlie the difficulties with cognitive flexibility in people with autism, Fenton says.

Strangers everywhere:

In August, researchers reported a connection between memory formation in the hippocampus and genetic risk for autism. They found that in mice, turning on or off certain autism-linked proteins contributes to neuronal changes thought to underlie learning and memory formation in the hippocampus[10].

One part of the hippocampus may be especially relevant for social behavior. Studies in mice suggest that this region, known as CA2, is crucial to social memory — an animal’s ability to recognize and remember details about members of its own species.

This area has a high concentration of receptors for **oxytocin, a hormone** involved in social

behavior and bonding. In a 2014 study in mice, a team led by **Richard Tsien** at New York University found that oxytocin directly **increases the activity of CA2 neurons** involved in establishing social memories.

In another study that year, a separate set of researchers engineered a mouse in which they could specifically silence CA2 neurons. The results were striking. The mice recognized familiar objects and found their way through a maze as adeptly as controls. And they were social, sniffing other mice placed in the same cage. But they lost their social memory: They treated mice they had met before as strangers, sniffing them just as much as they did new mice[1].

The role of the CA2 region in autism is not yet known. “Clearly the symptoms of silencing CA2 are not identical to the symptoms of autism where loss of sociability is one of the key findings,” says **Steven Siegelbaum**, professor of neuroscience and pharmacology at Columbia University in New York, who led the study. But problems with CA2 neurons could contribute to low social aptitude in autism, he says.

Siegelbaum’s team has found impaired CA2 function and social memory in a mouse model of 22q11.2 syndrome, a genetic disruption linked to schizophrenia and autism[11]. The researchers are investigating possible disruptions in the region in mice lacking the autism-linked genes **CNTNAP2**, **SHANK3** or **NRXN1a**. If changes in CA2 function are associated with autism features in the mice, the researchers plan to test whether increasing or decreasing the activity of neurons in this region alleviates these features, Siegelbaum says.

This sort of research raises the possibility that future treatments for autism could attempt to modify the function of specific types of hippocampal cells. In the meantime, people with autism may be able to use their solid grasp of facts to circumvent some difficulties. Many autism interventions draw on this strength, explicitly instructing children when to make eye contact or how to take turns rolling a ball back and forth.

“Declarative memory is a really powerful and flexible system,” Ullman says. “It can [be used to] learn all sorts of different compensatory strategies.”

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