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Why does brain development diverge from normal in autism spectrum disorders?

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Rett syndrome, a neurodevelopmental disorder on the autism spectrum, is marked by relatively normal development in infancy followed by a loss of loss of cognitive, social and language skills starting at 12 to 18 months of age. It is increasingly seen as a disorder of synapses, the connections between neurons that together form brain circuits. What hasn't been clear is why children start out developing normally, only to become progressively abnormal. New research from Children's Hospital Boston, published in the April 14 issue of *Neuron*, helps unravel what's going on.

The researchers, led by Chinfei Chen, MD, PhD, of Children's F.M. Kirby Neurobiology Center, studied synapse development in mice with a mutation in the Mecp2 gene, the same gene linked to human Rett syndrome. They found strong evidence that the loss of functioning Mecp2 prevents synapses and circuits from maturing and refining in response to cues from the environment – just at the time when babies' brains should be maximally receptive to these cues.

Chen believes her findings may have implications not just for Rett syndrome, but for other autism spectrum disorders. "Many ASDs manifest between 1 and 2 years of age, a period when kids are interacting more with the outside world," says Chen. "The brain of an autistic child looks normal, but there's a subtle difference in connections that has to do with how they process experiences. If you could diagnose early enough, there might be a way to alter the course of the disease by modifying experience, such as through intense one-to-one therapy."

Chen and colleagues focused on a synaptic circuit in the brain's visual system that is relatively easy to study, known as the retinogeniculate synapse. It connects the cells receiving input from the eye to the lateral geniculate nucleus, an important relay station in the brain's thalamus. Visual input from the outside world, during a specific "critical period," is crucial for its normal development.

The team tested the functioning of the circuit by stimulating the optic tract and measuring electrical responses in the thalamus to see how the neurons were connected, and how strong the connections were. In Mecp2-mutant mice, these recordings indicated that the visual circuit formed normally at first, and that during the second week of life, weaker connections were pruned away and others strengthened, just as they should be.

But after day 21 of life – after mice open their eyes and when the visual circuitry should be further pruned and strengthened based on visual experience – it became abnormal. The number of inputs and connections actually increased, while the strength of the synapses decreased.

This pattern was similar to that seen when normal mice were kept in the dark after day 21, depriving them of visual stimulation. Together, the findings suggest that Mecp2 is critically important to our ability to refine synaptic circuits based on sensory experience, says Chen. Without Mecp2, the circuit fails to incorporate this experience.

"During this last phase of development, you need sensory input to lock down and stabilize the connections," Chen explains. "But the circuit is not getting the right signal to stabilize, and continues to look around for the right connections."

In patients with Rett syndrome, the reduction in Mecp2 levels is especially striking in the thalamus, which processes and relays sensory

information to the cortex, where thought, memory and language reside. "It's very telling that we see these synaptic abnormalities in the thalamus, which is like a switchboard operator for the brain," says Chen. "A small disruption in the thalamus can radiate to large areas of the cortex."

This model of Rett syndrome is consistent with mouse models of other autism-related disorders like Fragile X and Angelman syndrome, which also show abnormalities during experience-dependent maturation of circuits, the researchers say.

"There could be a problem with how information is taken in," Chen says. "What's being perceived is different, so the response is different."

Chen and colleagues are now investigating whether reactivating Mecp2 at different times could improve organization of the visual circuitry.

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