NEWS

Brain’s center of automatic body functions has autism links

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Some people with autism have trouble **coordinating their movements**. Some experience sensory disturbances, such that everyday sounds seem **unbearably loud**. And some have an atypical heart rate or **disturbed sleep cycles**. These seemingly disparate features are all tied to a tiny region called the brainstem.

The brainstem is one of the first brain regions to form, during the first trimester — a time period **thought to be critical in autism**. Nestled in the nexus between brain and spinal cord, it serves as a relay center for motor and sensory information and coordinates the **autonomic nervous system**, which governs vital unconscious functions such as breathing, pulse and **sleep**. The brainstem also acts as a hub, connecting a variety of other brain areas implicated in autism.

“Thinking that [autism] is a condition of abnormal connectivity, then an area where a lot of the connections come together or travel through — we may see some abnormalities there,” says **Roger Jou**, instructor of clinical psychology at Yale University in New Haven, Connecticut.

Despite that logic, many researchers have been skeptical about looking for explanations for autism outside of the cortex, the brain area that orchestrates complex cognitive processes, says **Jonathan Delafield-Butt**, director of the Laboratory for Innovation in Autism at the University of Strathclyde in Scotland.

“Neuroscience has focused on the cortex and cortical function,” he says. “There’s been a huge amount of work on the cerebellum as well. The brainstem gets lost in between.”

Jou and Delafield-Butt are among a small group of autism researchers investigating whether disruptions in the development of the brainstem can perturb critical connections and cause, or at least contribute to, some autism behaviors.

Testing this theory is challenging because the brainstem's small size and location at the back of the head make it difficult to study. But improvements in imaging techniques and software are giving researchers more glimpses of the region. Adding heft to its connection to autism, studies are revealing disruptions in bodily functions that the brainstem controls such as **heart rate**, breathing and the sleep-wake cycle in people with the condition.

Unclear picture:

Theories about the brainstem's role in autism aren't new. In the early 1960s, researcher Bernard Rimland at the U.S. Navy hypothesized that a part of the brainstem that filters sensory perception was involved in some of autism's behavioral features, such as sensory sensitivities[1]. It was the first brain-based theory of autism's cause, but Rimland never tested it and it was soon forgotten. (Rimland later drew controversy by promoting the vaccine theory of autism and treatments such as chelation, which evidence does not support.)

In the 1980s and 1990s, a dozen or so postmortem brain tissue and imaging studies suggested that there are structural anomalies in the brainstems of autistic people, but the anomalies the studies described differed and they were sometimes contradictory[2,3,4].

Some of the discrepancies might have arisen at least partly because the brainstem is difficult to capture in brain images, says **Brittany Travers**, assistant professor of kinesiology at the University of Wisconsin-Madison. It is surrounded by major blood vessels and cerebrospinal fluid, which are in constant motion due to breathing and circulation and create **'noise' in images**. The region is also so tiny that long scans are needed to reveal any detail, and it contains multiple tissue types packed together in dense, complex arrangements. What's more, for a long time "no one was specifically setting out to image the brainstem," Travers says, so scanning software often distorted the region, cutting it off at the edge or warping its shape.

Still, several studies published over the past decade or so have begun to bring the brainstem into focus and suggest that its size or developmental trajectory is altered in people with autism. Preschool-aged children with autism may have enlarged brainstems, particularly those who also have intellectual disability, a research team reported last year[5]. Later in childhood, a different pattern may emerge: Between ages 8 and 12, autistic boys **have smaller brainstems** than their typical peers do, although their brainstem growth catches up by age 15, according to a pair of studies published in 2009 and 2013.

These size alterations often correspond to the severity of autism traits. Preteen autistic boys with more atypical brainstems also have more sensory sensitivities related to food taste and texture, the 2009 study showed. Children with autism who have smaller brainstems tend to have **more pronounced autism traits** overall, according to unpublished data Travers has collected.

The brainstem's white matter — the nerve fibers that connect brain regions — may be altered in

autistic people. Among boys and men with autism, those with more poorly organized white matter in the brainstem also have more severe autism traits and weaker grip strength, hinting at a link between the brainstem and motor problems in autism[6]. Other evidence suggests that autistic boys have less white matter in the brainstem than typical boys do, which tracks with poor performance on tests of motor skills[7].

Sound and sleep:

Increasing evidence that basic, automatic bodily functions are altered in people with autism is also bringing attention to the brainstem, which controls these processes. For instance, a number of studies suggest autistic people and their typical peers have different variations in their heart rates. Heart rate variability may reflect a person's ability to recognize social cues, one team found[8]. Likewise, multiple studies show that autistic people have **trouble falling and staying asleep**. And breathing difficulties seen in **children with Rett syndrome**, an autism-related genetic condition, may be linked to distinct circuits in the brainstem, a mouse study suggests[9].

The brainstem has a role in coordinating movement, and some researchers argue that its dysfunction could contribute to **motor problems in autism**. Autistic people show alterations in eye movements called saccades, which suggests problems integrating sensory and motor information in the brainstem[10]. And autistic people show atypical acceleration and deceleration when they perform simple movements, such as swinging an arm back and forth. This difference implicates a part of the brainstem called the inferior olive, which integrates the subsecond timing of movements[11].

Another part of the brainstem called the superior colliculus is a key player in visual attention. It receives information from the retina of the eye and coordinates attention to faces, biological movement, and reactions to emotional stimuli. Disruption of its development **could underlie difficulties** with these functions in autism, some researchers argue.

In addition, the brainstem contributes to processing sounds. Multiple studies over the past five decades have shown that the brainstem's **response to sound** tends to be smaller and slower in children with autism, or in infants later diagnosed with the condition[12]. As a consequence, "processing of speech sounds might take longer, and their path might be a little bit different in someone who has autism," says **Randy Kulesza**, director of anatomy at Lake Erie College of Osteopathic Medicine in Erie, Pennsylvania. This lag could in turn contribute to communication difficulties, he says.

Also, postmortem autism brains contain fewer auditory brainstem neurons, especially in a structure called the superior olive, than controls do, Kulesza and his team have found. And a response to sound **known as the stapedial reflex**, controlled by the brainstem, happens more slowly in children with autism and is triggered at lower volumes, they reported in 2013. This reflex difference

could contribute to hypersensitivity to sounds, and it or other brainstem responses to sound might be **used to screen infants** for autism[13].

These findings implicate many parts of the brainstem, but most imaging studies have looked only at the brainstem as a whole so far. “I think one of the key challenges right now is identifying the precise location of disruptions in the brainstem,” Delafield-Butt says.

Travers is collaborating with imaging specialists at the University of Wisconsin to develop new imaging software for taking a more detailed look at smaller structures within the brainstem. “I’m hoping we’re in this renaissance of looking at the brainstem,” Travers says. “Maybe we’ll look back 5 or 10 years from now and be like, ‘Wow, that brainstem really opened up doors.’”

*With additional reporting by **Hannah Furfaro***

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