Newly understood circuits add finesse to nerve signals

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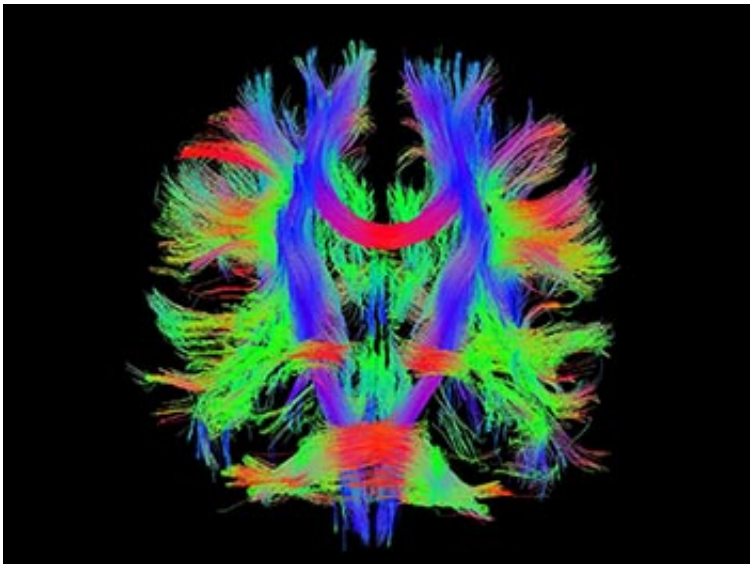

Brain circuits signal beyond the neat pathways shown in this nerve connectivity map. Image credit: Meredith Reid

(Medical Xpress)—An unusual kind of circuit fine-tunes the brain's control over movement and incoming sensory information, and without relying on conventional nerve pathways, according to a study published this week in the journal *Neuron*.

Researchers at the University of Alabama at Birmingham (UAB) discovered new details of a mechanism operating in the cerebellum, the brain region that processes nerve signals coming in from the spinal cord

and cortex.

"Our results explain a second layer of nerve signal transmission that depends, not on whether a nerve cell is wired into a defined signaling pathway circuit, but instead on how close it is to the pathway," said Jacques Wadiche, Ph.D., assistant professor in the Department of Neurobiology within the UAB School of Medicine, investigator in the Evelyn McKnight Brain Institute at UAB and senior study author. "It has become clear that this kind of nerve circuit is intimately linked with autism and certain movement disorders, and we hope the mechanisms detailed here contribute to the design of new treatments."

Beyond nerve pathways

Nerve cells are known to occur in defined pathways that transmit messages in one direction. This pathway-specific view of nerve signaling has been reinforced by high-tech imaging studies yielding detailed connectivity maps. Along these lines, the Obama Administration will soon ask Congress for $100 million in research funding to further improve such maps.

Within nerve pathways, each nerve cell sends an electric pulse down an extension of itself called an axon until it reaches a synapse, a gap between itself and the next cell in line. When it reaches an axon's end, the pulse triggers the release of chemicals called neurotransmitters that float across the gap, where they either cause the downstream nerve cell to "fire" and pass on the message, or stop the message. In this way, each synapse between nerve cells in a pathway "decides" whether or not a message continues on.

In recent years, studies have found that neurotransmitters also spill into tissue surrounding axons in a type signaling not restricted to synaptic connections. With the term itself implying a mess, "spillover" was

thought to degrade the capacity of nerve cells to precisely pass on signals.

The current study adds to recent evidence arguing that spillover may instead enhance message transmission, with the results revolving around three nerve cell types in the cerebellum: climbing fibers, Purkinje cells and interneurons.

Climbing fibers, which carry information from the brainstem into the cerebellum, play key roles in motor timing and sensory processing. Within these fibers, nerve cells release the excitatory neurotransmitter glutamate into synapses that then strive to pass messages deeper into the cerebellum. Purkinje cells are paired with climbing fibers and intent on inhibiting their signals.

When excited by glutamate from climbing fibers at one end, Purkinje cells release another neurotransmitter called GABA at their downstream synapse to stop the message. An excitatory signal triggers an inhibitory one as a counter-balance, a form of feedback critical to the function of the central nervous system. Lack of inhibition, for instance, causes circuits to seize, seizures and the death of Purkinje cells, the latter of which has been linked by post mortem studies to a higher incidence of autism spectrum disorders.

Previously, researchers thought that incoming signals from climbing fibers caused a single, strong response in the cerebellum: the activation of Purkinje cells that released GABA. The current study argues that such signals also trigger the firing of interneurons, nearby inhibitory middlemen that connect sets of nerve cells.

Interneurons within, and outside of, the glutamate spill zone around climbing fibers may have different effects on the other interneurons and Purkinje cells they connect to, according to the current finding. The

interactions either inhibit or excite many Purkinje cells surrounding an active climbing fiber and refine its messages in a feedback system more sophisticated than once thought.

Glutamate has its effect by fitting into AMPA and NMDA receptor proteins, like a key into a lock, on the surfaces of nerve cells it signals to. The consensus has been that glutamate receptors occur only within synapses. Finding them on nerve cells outside of synapse-defined pathways represents "a fundamental shift in understanding," said Wadiche, and may result in longer-lasting inhibition within key signaling pathways.

"A 2007 study published in *Nature Neuroscience* found that many climbing fibers signal to interneurons in the outer layer of the cerebellum outside nerve pathways and exclusively through glutamate spillover," said Luke Coddington, a graduate student in Wadiche's lab and study author. "Our team built on that observation to show how spillover affects the function of interneurons, Purkinje cells, and ultimately, the entire cerebellum. Spillover-mediated signaling recruits local microcircuits to extend the reach and finesse of climbing fiber signaling."

Provided by University of Alabama at Birmingham