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A comprehensive circuit mapping study reveals many unexpected facts about the norepinephrine neurons in the brainstem

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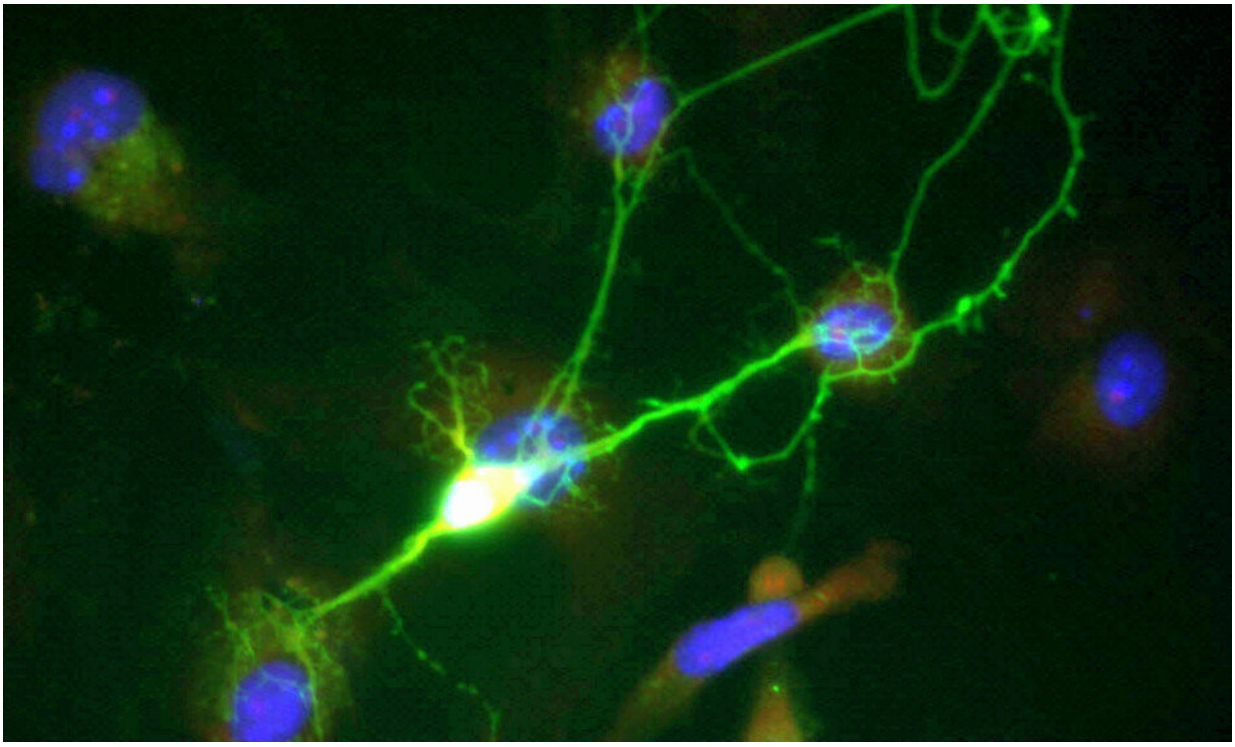

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A small nucleus in the brainstem called locus coeruleus (literally the "blue spot,") is the primary source of a major neuromodulator, norepinephrine (NE), an important mediator of the 'fight or flight'

response in animals. However, very little is known about the local connections of this small albeit critically important group of neurons. A recent pioneering study published in *eLife* from the laboratory of Dr. Xiaolong Jiang, investigator at the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas Children's Hospital and assistant professor at Baylor College of Medicine, now reveals the cellular composition and circuit organization of the locus coeruleus in adult mice.

"In this study, we undertook the arduous task of mapping local connections of NE-producing neurons in the locus coeruleus," Dr. Jiang said. "This is the first study of such an unprecedented magnitude and detail to be performed on the locus coeruleus, and in fact, on any monoamine neurotransmitter system. Our study has revealed that the neurons in the locus coeruleus have an unexpectedly rich cellular heterogeneity and local wiring logic."

Locus coeruleus senses danger and alerts other brain regions

Locus coeruleus (LC) is known to house the vast majority of norepinephrine-releasing neurons in the brain and regulates many fundamental brain functions including the fight and flight response, sleep/wake cycles, and attention control. Present in the pontine region of the brainstem, LC neurons sense any existential dangers or threats in our external environment and send signals to alert other brain regions of the impending danger.

The primary action of LC neurons is to release norepinephrine, a neurotransmitter, and a hormone, that increases alertness and promotes arousal, regulating the sleep/wake cycle and memory. Altered levels of norepinephrine are associated with depression, anxiety, post-traumatic

stress disorder, panic attacks, hyperactivity, heart problems, and substance abuse. Thus, a better understanding of how LC neurons function is key to understanding and identifying therapies for many neuropsychiatric and neurodegenerative conditions.

Locus coeruleus has two distinct cellular subtypes, homotypically connected via gap junctions

Once viewed as a homogenous group of neurons that exert global, uniform influence over the entire brain, recent studies suggest LC neurons are a heterogeneous population of noradrenergic cells that exhibit both spatial and temporal modularity. These findings piqued the interest of Dr. Jiang and his team to investigate the cellular and circuit mechanisms underlying the functional diversity of LC neurons.

To do that, the team had to overcome a few technical barriers to be able to measure the activity of several LC neurons simultaneously from the brain slices of adult mice. For instance, while the technique of intracellular recordings of more than two neurons simultaneously has been used to study cortical circuits for the past few decades, it has been challenging to use this technique to record small nuclei in the brainstem such as the LC due to the space restraint and limited cell number in each brain slice. In this study, by optimizing slice quality and adapting their recording system to small brainstem slices, Andrew McKinney, a graduate student in the Jiang lab and the first author of the paper, successfully managed to record up to eight LC neurons simultaneously for the first time.

This technical development led Andrew and others in the team to make several unexpected observations about how LC neurons are organized and how they function.

First, consistent with emerging views in the field they found that norepinephrine-producing neurons in the LC are diverse. Further, they found that these can be classified into at least two major cell types based on their morphology and electrical properties and these subtypes occupy different spatial locations (anatomical niches) within LC. This finding provided a solid and much-needed basis for further in-depth studies of LC in adult animals.

Second, they found that LC neurons do not form chemical synapses, the most common type of connection between neurons. Instead, they form electrical synapses and connect to one another via gap junctions. This was an unexpected discovery because the conventional thinking is that electrical coupling via gap junctions is primarily present in developing LC and not in the LC of adult animals.

Third, they found that LC neurons of the same subtype electrically connected with one another but did not connect with the neurons of the other kind, providing the first cellular and circuit clue for the functional modularity of the LC and opening up avenues to understand how functional modularity arises within the noradrenergic system and dynamically controls diverse processes. These findings indicate that given that each cell type has preferential anatomical locations in LC and different projection targets, each electrically coupled within-cell-type homotypic network may coordinate or synergize their input or output as a whole to engage in distinct functions of the circuits as they carry information from the brain to various targets such as muscles or glands.

Finally, unlike the web-like connections that are typical of chemical synapses between neurons in the central nervous system, LC neurons of a single subtype were discovered to form unique linear chain-like electrical connections with one another. This provides the first experimental clue into how electrically-coupled neuronal networks are organized in the brain.

"This study sheds light on several unexplored questions about the cellular and circuit organization of the locus coeruleus in particular and also offers several new insights into other broader aspects of brain physiology," Dr. Jiang said. "We anticipate these novel findings will be of broad interest to cellular, systems, and computational neuroscientists and will inspire several future studies to understand how each neuron within LC interacts with one another to give rise to a synchronized network," Dr. Jiang added. "In addition, given that the dysregulation of the LC has been implicated in many neuropsychiatric and neurodegenerative disorders including autism and Alzheimer's disease, these findings provide an essential knowledge base to decipher cellular and circuit mechanisms of these diseases."

Others involved in the study were Ming Hu, Amber Hoskins, Arian Mohammadyar, Nabeeha Naeem, Junzhang Jing, Saumil Patel, and Bhavin Sheth. They are affiliated with one or more of the following institutions: Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, Baylor College of Medicine, and the University of Houston. The study was supported by several research and training grants from the National Institutes of Health and the Main Street America Fund.

More information: Andrew McKinney et al, Cellular composition and circuit organization of the locus coeruleus of adult mice, *eLife* (2023). DOI: 10.7554/eLife.80100

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