Using gene expression data to map the mouse brain

By Robin Arnette

If you're planning a fun-filled weekend of hiking and camping, bringing along a map of the area is a good idea. What would happen, though, if that map included mountains and lakes of the terrain, but lacked roads, bridges, and footpaths? Finding your way around the landscape wouldn't be impossible. Yet, knowing how everything connected would make the adventure more enjoyable.

Scientists in the NIEHS Developmental Neurobiology Group, led by Patricia Jensen, Ph.D., had a similar problem, when they began studying a set of neurons in the brainstem of adult mice. These neurons make and release norepinephrine (NE), a molecule that acts as a hormone and neurotransmitter. Jensen knew, in general, their form and structure, and where NE neurons were positioned, but nothing about their cellular organization or the neural highways they used to communicate with different regions of the brain.

Jensen is the newest member of the NIEHS Laboratory of Neurobiology, joining the Institute in 2009. (Photo courtesy of Steve McCaw)

Jensen's work appeared online *(http://www.ncbi.nlm.nih.gov/pubmed/23852112)* July 14 in Nature Neuroscience, and revealed, for the first time, a roadmap of NE neurons in the rodent brain. Since these nerve cells are involved in a wide range of behaviors and physiological processes, such as maintaining attention, sleep, food intake, and memory, the research has important implications for conditions as varied as Parkinson's disease and mental health disorders.

Tracking NE neurons and their connections

Prior to this work, neuroscientists categorized NE neurons into six separate nuclei, or groups based on their anatomical structure, in the adult mouse brain. But, Jensen's team developed a novel way to classify NE neurons based on the gene expression differences they exhibit during early mouse development.

Jensen explained that the hindbrain of a fetal mouse, like that of a human fetus, is divided into 8 segments called rhombomeres, each of which expresses a unique combination of genes. Adult NE neurons that are derived from a particular rhombomere will have the same gene expression pattern (see illustration). With this information, Jensen now has the ability to manipulate various classes of NE neurons in mice and study the behavioral consequences.

"Dividing NE neurons according to gene expression differences shows how diverse this small population of neurons is," Jensen said. "We hope to gain insight into why certain populations of NE neurons may be vulnerable to environmental insult or disease."

Robertson is a postdoctoral fellow in Jensen's group, and was one of 19 NIEHS trainees who received a 2014 NIH Fellows Award for Research Excellence (FARE). The award provides recipients with funds to travel to a scientific meeting of their choice. (Photo courtesy of Steve McCaw)

Two members of Jensen's lab, Sabrina Robertson, Ph.D., and Nicholas Plummer, Ph.D., shared first authorship of the paper, and said the article shattered another long-held belief in the field. Neuroscientists presumed that all of the NE released in the cortex - the outer furrowed portion of the brain important in higher-order thinking - came from one cluster of NE neurons in the locus coeruleus (LC), a small section of the brainstem that processes the body's sensory signals. They found that other NE neurons, outside of the LC region, communicate with the cortex as well.

"We observed that certain subpopulations of NE neurons were talking to different regions of the brain, which suggested the gene expression pattern of a nascent NE neuron may contribute to the function of that NE neuron in the adult," Robertson said.

NE neurons implicated in human disease

Researchers have implicated NE neuron dysfunction in a number of mental health disorders, and have determined that NE neurons are lost in Parkinson's disease, Alzheimer's disease, and Down syndrome, also known as trisomy 21. These neurons are also disrupted following exposure to toxicants, such as 1-bromopropane or ozone.

Because of the influence NE neurons have on the brain, pharmaceutical companies have manufactured products that focus on

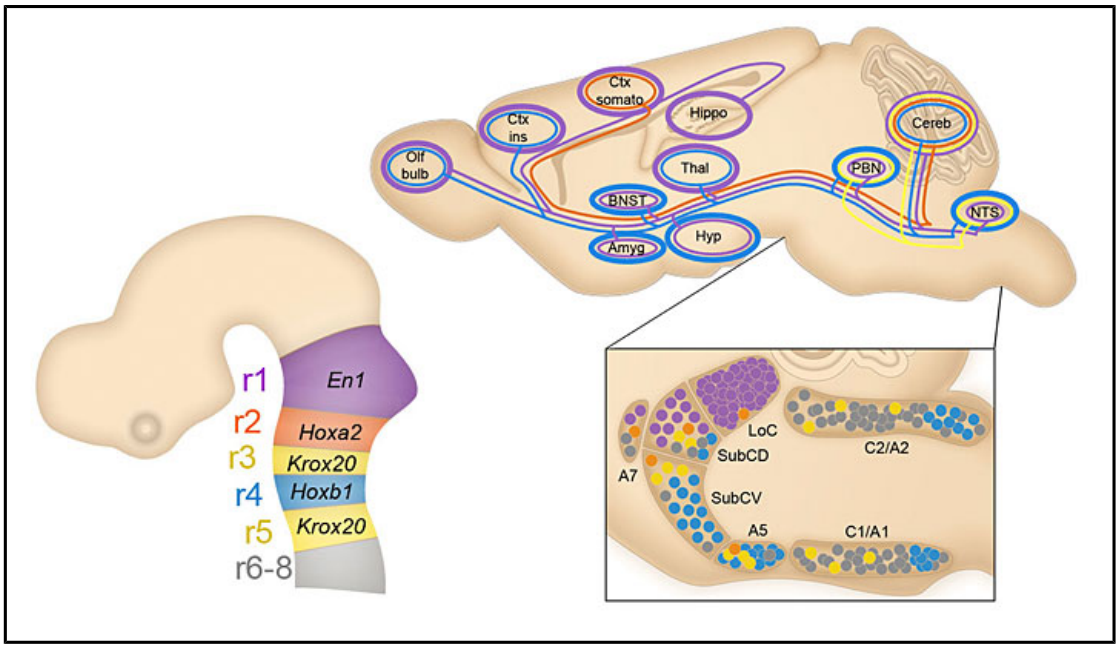
their activity. Several medications on the market today, such as antidepressants and prescriptions for attention deficit hyperactivity disorder, target NE neurons.

With this new NE neuron roadmap, Jensen and other neuroscientists will be able to navigate through the brain, on a journey to better treatments for neurological disorders.

Citation: Robertson SD, Plummer NW, de Marchena J, Jensen P.
(http://www.ncbi.nlm.nih.gov/pubmed/23852112)
2013. Developmental origins of central norepinephrine neuron diversity. Nat Neurosci; doi:10.1038/nn.3458 [Online 14 July 2013].

As a staff scientist in Jensen's group, Plummer helps supervise the various research projects taking place in the lab. (Photo courtesy of Steve McCaw)

Jacqueline de Marchena, Ph.D., a postdoctoral fellow who works with Jensen, is also a co-author on the paper. de Marchena was a 2013 FARE award winner. (Photo courtesy of Steve McCaw)



Using a technique called genetic fate mapping, Jensen's team labeled NE neurons in the fetal mouse brain, and tracked their progress during development. The graphic on the left shows the fetal brain with rhombomeres 1-8 distinguished by color, along with the expression of specific genes. The image on the right displays an adult mouse brain, which includes the location of rhomobomere-derived NE neurons in the hindbrain (inset box). The colored lines in the upper portion depict the NE neuronal projections throughout the brain. (Design and artwork by Patricia Jensen, Sabrina Robertson, and Sue Edelstein)

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