NEUROANATOMY

What makes us human? Newly discovered neurons may be the key

Boldog et. al. have discovered a specialized GABAergic interneuron subtype within layer 1 cortex unique to the human brain. These rosehip interneurons have been shown to target layer 3 pyramidal neurons and work to inhibit back propagating, expressing great local control of distal dendrites.

Jessica Faraca

What is it that makes the human brain unique compared to other animals? This is a question many neuroscientists are interested in, especially when it comes to human's capacity for higher cognitive functioning. The work of Boldog et.al.[1] may be the clue needed to crack our understanding of the human brain. In their recently published article in Nature Neuroscience, Boldog et. al. share the discovery of a new neuron subtype unique to humans. These newly found cells, called rosehip neurons due to their shape, are found within layer 1 cerebral cortex. What makes these cells so interesting is their morphology and physiology, which is unlike anything found within rodent cortex. With the discovery of these interneurons insight can be gained as to how inhibition impacts cortical function of human cognition, and potentially how human cortex differs from other species.

Understanding the function and type of neurons within the cerebral cortex has been of interest since the time of Santiago Ramón y Cajal, and his findings supporting the neuron doctrine[2]. Traditionally, when studying the mechanisms of our brains it is not uncommon to use animal models. Previously neuroscientist believed the variation in human and animal brains were only a result of their differing size and degree of elaboration[3]. The idea of variation in type of cells between species was not an idea widely held. However, as research techniques have advanced our ability to identify differences in neurons has increased drastically. One approach to researching cognition that has been garnering attention recently is a combination between genetics and cognitive neuroscience[4]. Through this new integrative research, it has been suggested that the synapse is an excellent starting point for global systems biology of the brain[5]. However, up until the findings of Boldog et.al. there was little evidence supporting differences between the types of neurons seen in humans compared to those of animals.

A typical approach for studies focusing on neurons of the neocortex is to complete electrophysiological recordings of brain slices. The electrophysiology of a cell provides information on the electrical behavior of neurons and the function of neural systems[6].However, only completing an electrophysiology study does not consider other aspects of cortical interneurons. To gather a comprehensive understanding, the cells morphology was also investigated. Distinctions between various neurons in terms of their dendritic configuration, axonal structures, and shape/size of soma can indicate variations in function and type of neuron[7]. To detect genetic links between cortical interneurons the study utilized single nucleus RNA-sequencing technology. With RNA sequencing it is possible to identify known markers which can

then be used to classify neuronal subtypes[8,9]. The objective of the project was to identify, and classify, neurons previously undiscovered. Boldog et.al. employed multiple methodologies, recording the cells electrophysiology, morphology, as well as sequencing single nucleus RNA allowing for thorough analysis of postmortem human cortex.

The team of researchers were able to identify GABAergic neurons of layer 1 via RNA-sequencing, which yielded cells aligning with known genetic markers. From these cells further, analysis and viewing was completed using a light microscope. In viewing the layer 1 GABAergic neurons an undescribed group of interneurons with large, rosehip-shaped axonal boutons forming compact arborizations were revealed. These rosehip cell boutons had an average measured volume approximately four times greater than that of neurogliaform cell boutons. After identifying these rosehip cells, mouse cortex was screened for similar genetic markers yielding no results, suggesting the type of neuron is specific to human cortex. Electrophysiology revealed rosehip cells had a lag that exceeded those of neurogliaform cells when responding to hyperpolarizing current pulses. It was found that rosehip interneurons received local excitatory inputs from layer 2/3 pyramidal cells, as visualized in Figure 1. the axons of layer 1 rosehip cells synapse with pyramidal cells in layer 3, providing inhibitory control via the release of GABA. These findings suggest that rosehip cells might specialize in the control of dendritic signal processing.

The findings of Boldog et. al. highlight how little is truly known about the human brain. Rather than prior propositions suggesting the relative size of neocortex is what differentiates human from animal, the discovery of rosehip interneurons implies there is more to the story. Instead of merely focusing on the gross anatomy, variations on the cellular level should be accounted for as well. Identifying these differences in cells and neural systems is a start to understanding the complex organ that is the brain. However, further research will need to be conducted analyzing what the implications of this inhibitory control means in respect to cognition.

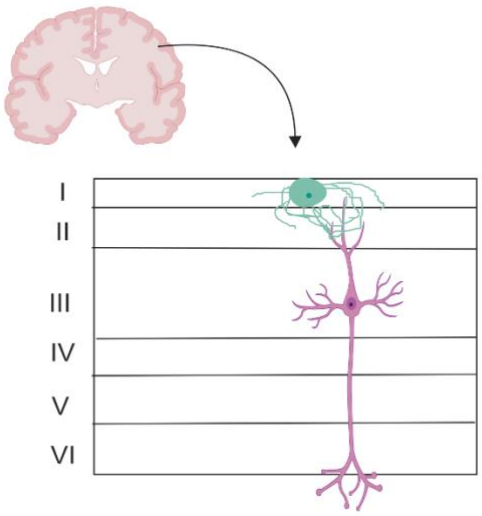

Figure 1. Depiction of newly discovered layer 1 rosehip interneurons (a) projecting to layer 3 pyramidal cells (b). Rosehip neurons synapse with dendrites of pyramidal cells expressing inhibitory control of cortical neurons.

REFERENCES

1. Boldog, Eszter, Trygve E. Bakken, Rebecca D. Hodge, Mark Novotny, Brian D. Aevermann, Judith Baka, Sándor Bordé, Jennie L. Close, Francisco Diez-Fuertes, Song-Lin Ding, Nóra Faragó, Ágnes K. Kocsis, Balázs Kovács, Zoe Maltzer, Jamison M. Mccorrison, Jeremy A. Miller, Gábor Molnár, Gáspár Oláh, Attila Ozsvár, Márton Rózsa, Soraya I. Shehata, Kimberly A. Smith, Susan M. Sunkin, Danny N. Tran, Pratap Venepally, Abby Wall, László G. Puskás, Pál Barzó, Frank J. Steemers, Nicholas J. Schork, Richard H. Scheuermann, Roger S. Lasken, Ed S. Lein, and Gábor Tamás. "Transcriptomic and Morphophysiological Evidence for a Specialized Human Cortical GABAergic Cell Type." *Nature Neuroscience*21, no. 9 (August 27, 2018): 1185-195. doi:10.1038/s41593-018-0205-2.
2. "The Nobel Prize in Physiology or Medicine 1906." NobelPrize.org. Accessed April 18, 2019. https://www.nobelprize.org/prizes/medicine/1906/cajal/biographical/.
3. Preuss, Todd M. "Taking the Measure of Diversity: Comparative Alternatives to the Model-Animal Paradigm in Cortical Neuroscience." Brain, Behavior and Evolution 55, no. 6 (2000): 287-99. doi:10.1159/000006664.
4. De Geus, E. J. C., & Boomsma, D. I. (2001). A genetic neuroscience approach to human cognition. European Psychologist, 6(4), 241-253. http://dx.doi.org/10.1027//1016-9040.6.4.241

5. "Systems Biology in Neuroscience: Bridging Genes to Cognition." Current Opinion in Neurobiology. October 04, 2003. Accessed April 18, 2019. https://www.sciencedirect.com/science/article/abs/pii/S0959438803001375.
6. Suter, Kelly J., Bret N. Smith, and F.edward Dudek. "Electrophysiological Recording from Brain Slices." Methods 18, no. 2 (1999): 86-90. doi:10.1006/meth.1999.0761.
7. "Petilla Terminology: Nomenclature of Features of GABAergic Interneurons of the Cerebral Cortex." Nature Reviews Neuroscience 9, no. 7 (2008): 557-68. doi:10.1038/nrn2402.
8. Krishnaswami, Suguna Rani, Rashel V. Grindberg, Mark Novotny, Pratap Venepally, Benjamin Lacar, Kunal Bhutani, Sara B. Linker, Son Pham, Jennifer A. Erwin, Jeremy A. Miller, Rebecca Hodge, James K. McCarthy, Martijn Kelder, Jamison McCorrison, Brian D. Aevermann, Francisco Diez Fuertes, Richard H. Scheuermann, Jun Lee, Ed S. Lein, Nicholas Schork, Michael J. McConnell, Fred H. Gage, and Roger S. Lasken. "Using Single Nuclei for RNA-seq to Capture the Transcriptome of Postmortem Neurons." Nature News. February 18, 2016. Accessed April 18, 2019. https://www.nature.com/articles/nprot.2016.015.
9. Lake, B. B., R. Ai, G. E. Kaeser, N. S. Salathia, Y. C. Yung, R. Liu, A. Wildberg, D. Gao, H.-L. Fung, S. Chen, R. Vijayaraghavan, J. Wong, A. Chen, X. Sheng, F. Kaper, R. Shen, M. Ronaghi, J.-B. Fan, W. Wang, J. Chun, and K. Zhang. "Neuronal Subtypes and Diversity Revealed by Single-nucleus RNA Sequencing of the Human Brain." Science 352, no. 6293 (2016): 1586-590. doi:10.1126/science.aaf1204.