

New method adds missing functionality to brain organoids

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Credit: Human Brain Project

In a collaborative study between Case Western Reserve University School of Medicine, the New York Stem Cell Foundation (NYSCF) Research Institute, and George Washington University, researchers have developed a new procedure for generating miniature 3-D versions of the brain called "organoids" from human stem cells. By providing an

environment for cells to interact the way they would in an actual human brain, brain organoids allow researchers to observe brain development, study disease, and test promising new drugs. The new technique, published online today in *Nature Methods*, creates the first organoids capable of myelination, modeling the brain's structure and function more closely than ever.

"NYSCF is committed to accelerating treatments for neurological diseases, and developing better ways for the community to use [stem cells](#) for disease research is a key part of achieving that goal," says Susan L. Solomon, NYSCF CEO. "This new method grew out of a longstanding collaboration enabled by the NYSCF community, and we are incredibly proud of the work that has resulted from this partnership."

The study was led by NYSCF—Robertson Stem Cell Investigator Alumnus Paul Tesar, Ph.D., the Dr. Donald and Ruth Weber Goodman Professor of Innovative Therapeutics and associate professor of genetics and genome sciences at Case Western Reserve University School of Medicine. The work at the NYSCF Research Institute was led by Valentina Fossati, Ph.D., NYSCF Senior Principal Investigator, who has collaborated with Dr. Tesar for years on unlocking the secrets of diseases like multiple sclerosis. Their collaboration began in 2011 through a conversation at the annual NYSCF Innovators Retreat, one of NYSCF's many endeavors to build bridges in the research community.

"When Dr. Tesar and Dr. Fossati first met at the NYSCF Innovator Retreat, the scientific sparks started to fly immediately," noted Solomon. "As this study shows, these types of collaborations are crucial for accelerating research and treatments."

Brain organoid technology has revolutionized the field by recapitulating the organization of different brain cell types, but previous organoids were missing one key ingredient: oligodendrocytes. Oligodendrocytes

are brain cells that produce myelin, a substance that coats nerve fibers and helps neurons send signals. When myelin is damaged, cells cannot communicate with each other as efficiently, leading to symptoms such as numbness, loss of reflexes, uncoordinated movement, and pain. In conditions where myelin is lost, such as multiple sclerosis or spinal cord injury, oligodendrocytes are believed to play an important but poorly understood role. Incorporating oligodendrocytes capable of myelination into organoid models offers a new way to study how this process goes awry in these diseases—and to test ways to repair it.

Building on a previous protocol originally developed at the NYSCF Research Institute to generate oligodendrocytes from stem cells, the team at Case Western Reserve identified a specific combination of growth factors that could generate organoids that included oligodendrocytes. They demonstrated that myelin-enhancing drugs increased myelination by oligodendrocytes in the organoids, suggesting that these organoids could be useful in preclinical tests of drugs to repair faulty myelination. The researchers also used this method to generate organoids from stem cells of patients with Pelizaeus-Merzbacher disease—a rare but fatal genetic myelination disorder—demonstrating that the [organoids](#) successfully modeled the characteristics of the disease. NYSCF researchers replicated the protocol independently using a different stem cell line, which was critical to demonstrate reproducibility.

"Our new method gives us a clearer picture of how brain [cells](#) are functioning and interacting in diseases like multiple sclerosis or Pelizaeus-Merzbacher, and it holds great promise for the development of new therapies to restore myelination," explains Dr. Tesar. "I look forward to continuing our collaboration with the NYSCF Research Institute towards better understanding and treatment of myelination disorders."

Dr. Tesar and Dr. Fossati's teams will put this new organoid protocol to work in future multiple sclerosis research, to test the effectiveness of drugs that target oligodendrocytes in an effort to stimulate myelination. Part of this work will be supported in the next three years by funding from New York State Stem Cell Science (NYSTEM). Dr. Tesar also received the 2017 NYSCF—Robertson Stem Cell Prize in recognition of his pioneering work in stem cell research for neurological diseases. His NYSCF funding was among several awards that enabled the current study.

"We're grateful for our fruitful collaboration with Dr. Tesar and thrilled that we were able to provide validation for this important technique to ensure it can be adopted by the community," says Dr. Fossati. "By filling a crucial gap in brain organoid models, we believe this new protocol will elevate research into [multiple sclerosis](#) as well as a variety of complex neurological disorders, including Alzheimer's disease and Parkinson's disease."

More information: Mayur Madhavan et al, Induction of myelinating oligodendrocytes in human cortical spheroids, *Nature Methods* (2018). [DOI: 10.1038/s41592-018-0081-4](https://doi.org/10.1038/s41592-018-0081-4)

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