Off the BENCH

02
17

The Eppendorf – LifeScienceStyle Magazine

p. 6 Brain Research in the Third Dimension

presented by eppendorf

A passion for science
Madeline Lancaster researches at the MRC Laboratory of Molecular Biology in Cambridge

“I am living my *dream.*”

What Makes us Human?

RESEARCH CAREERS

Madeline Lancaster, cell biologist at the MRC Laboratory of Molecular Biology in Cambridge, has developed a technique allowing her to create mini brains from cell cultures. These incredible organoids, no larger than the eraser at the end of a pencil, serve as a model for Madeline's research into early human brain development and are enabling Madeline and her team to tackle the age-old question: what is it that distinguishes us as humans?

Object of desire
The mini brain from the Petri dish

"I love when I have an experiment going and the first thing I want to check in the morning is the result of the experiment," Madeline says. Her research is aiming to determine what is special about our brains and what gives us our unique intellectual abilities. "We focus on how human neurons are made and try to understand what's different about that process in humans compared with primates and other animals."

Studying an organ which has been described as "the most complex thing in the universe" is a tall order, but Madeline knows what keeps her motivated: "to make a discovery that no one else has ever made. To find something out that nobody has ever seen before and you get to tell the world about it. That thrill of discovery is really unique."

A child's dream come true

Madeline has been interested in the human brain ever since she was a child, when she first saw a neuron down a microscope in her father's lab. "And my mother is a psychiatrist, which is perhaps also where my interest in the brain comes from," Madeline explains. Apart from a temporary lapse as a teenager when Madeline dreamed of a career as an astronaut, she has always known what she wanted to be when she grew up: "actually, for as long as I can remember, I wanted to be a scientist."

Madeline grew up in Salt Lake City, Utah, and after High School moved to Los Angeles where she studied biochemistry at Occidental College. Pursuing her dream to become a scientist, Madeline then joined the lab of Professor Joseph Gleeson at the University of California, San Diego, one of the world's leading public research universities. Here, Madeline researched the brains of mammals and earned her PhD in 2010.

Madeline went on to join the Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA), Vienna, as a postdoctoral researcher in Professor Jürgen Knoblich's lab. ►

Committed and successful
In 2014, Madeline Lancaster received the Eppendorf Award for Young European Investigators

Madeline conducted experiments with neuronal stem cells: "we started by looking at them in a dish and while I was playing with various culture conditions I stumbled upon this method of culturing the cells in 3D to generate these really beautiful self-organizing brain tissues." Madeline had achieved something that until then had evaded all other scientists: cultivating complex neuronal tissue from pluripotent stem cells.

Young and decorated

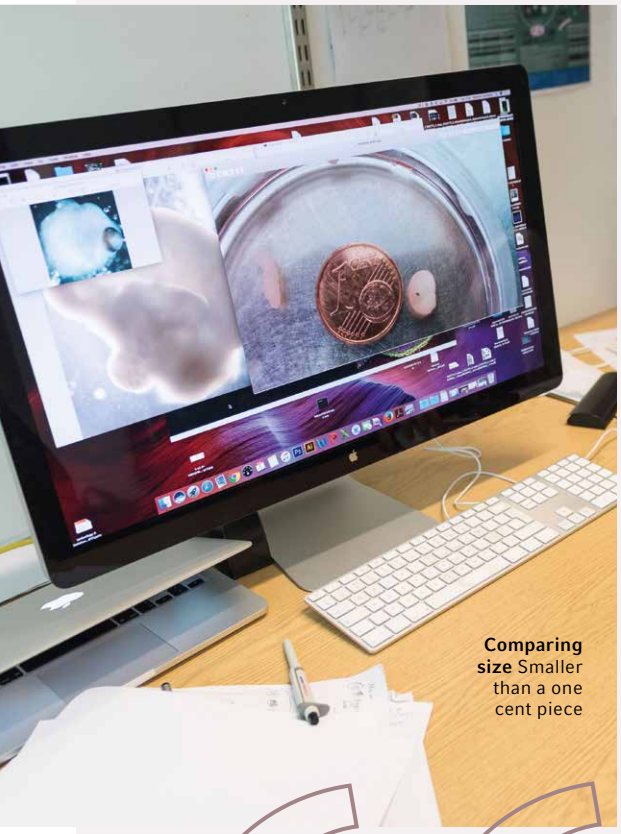
For the very first time, using these mini brains which are equivalent in developmental timing to an embryonic brain in the ninth week of pregnancy, structures of the brain could be recreated: the *cerebral cortex*, the retina, the *hippocampus* and the *choroid plexus*, a region in which the cerebrospinal fluid is produced. This breakthrough catapulted the 35-year-old into the top ranks of the scientific community. She received global recognition and numerous awards, including the 2014 Eppendorf Award for Young European Investigators.

Madeline is now a Group Leader at the MRC Laboratory of Molecular Biology, Cambridge. She places great importance on the work of her team and being surrounded by committed, enthusiastic colleagues. "I think the best motivation comes from within," Madeline says. "We can support that motivation, but those with the most likelihood of success, I think, are highly intrinsically motivated. It's wonderful to see that drive in my younger colleagues and I try to nurture that in myself and others as best I can."

How does Madeline manage the contrasting responsibilities of a demanding family life – she has two small children – and an even more demanding job? "My partner is really instrumental in allowing me to have both a family and my career," Madeline explains. "We really share the responsibilities of the children, the house, and so on. If it wasn't for my husband I wouldn't be able to do it."

Taking a close look
The microscope as a daily work utensil

Four millimeters maximum The mini brain as an object for great insights



Comparing size Smaller than a one cent piece

"All we do is support the cells and keep the tissue healthy with the right combination of nutrients, and these tissues essentially build themselves."

Thanks to this, Madeline can continue her ground-breaking research using her three-dimensional brain models. She focuses on diseases, such as a genetic form of microcephaly – a condition which results in an individual having a much smaller brain. Madeline and her team discovered that the disease is caused when neuronal stem cells prematurely switch to the production of neurons leading them to exhaust too soon, thus producing overall fewer neurons and a smaller brain.

Miniature brain at high value

"The human brain is equipped with vast developmental possibilities that have so far been difficult to study using traditional animal models," Madeline explains. The study of schizophrenia or autism using mice is problematic. Not only is the human brain home to far more stem cells than the mouse brain, but the behavior of human stem cells is different to those found in mice. This illustrates the incredible value of Madeline's mini brains for research, but she modestly says that their creation is rather simple: "it's really quite remarkable that these tissues can develop by themselves with only little external intervention. Really all we do is support the cells and keep the tissue healthy with the right combination of nutrients, and these brain tissues essentially build themselves."

Some of us may regard a brain grown in the lab with suspicion. Should we worry? Madeline diffuses concern with a smile, "what we created is a piece of brain tissue without connections and without sentience." This organoid could never achieve the complexity of a brain because, amongst other constraints, it lacks blood circulation. Oxygen and nutrients in the culture medium must reach the neurons in the mini-brain by simple diffusion. This places a size limit on the organoids, meaning they cannot grow larger than four millimeters.

Following the spectacular creation of a three-dimensional imitation of the human brain, is there still some sort of research jackpot to reach? Madeline smiles, "the most exciting finding would be if we could identify a unique trait of human neural stem cells, and then see if we could recapitulate that trait in a non-human cell type. That would be the ultimate evidence that we have hit on something real."

Life in the lab is busy, but Madeline is content, "honestly, I am living my dream! I just have fun doing exciting experiments, and I will be happy if I can just continue to have that freedom to do discovery-based research." ■

THERE'S MORE: Visit the website

http://bit.ly/2hqy0HO

The brain – a high-performance organ
To keep it fit for a long time, you must not forget how to learn

It's All in Your Head

Firing neurons, useful errors: how we learn and why mistakes made by our brains are a prerequisite for creativity and fresh ideas.

Every day we are inundated with countless pieces of information, images and news. Interruptions from vibrating phones or push news on social media can certainly compromise our ability to concentrate. A study conducted by the psychologist Erik Altmann of Michigan State University shows: the performance of the brain is reduced by 20 to 40 percent if tasks are completed in parallel rather than sequentially. For the purpose of this study, 300 subjects were asked to solve problems requiring attention using a computer. Half of the participants were required to repeatedly type two letters into their smart phones. While the interruption only took 2.8 seconds, it led to a doubling of the error rate compared to those participants working without interruption. The explanation offered by the research team: distraction from one task in order to perform another triggers a disruption – independent of the

"Learning and memory are based on the combination of very simple processes."

"To keep the brain sharp, it is important not to forget to learn."

duration of the interruption. After all, those who wear blinders at all times will never be able to see beyond their own noses.

Distractions, multitasking and digital media are part and parcel of most peoples' everyday existence. "One of the most prominent weaknesses of our brain is its penchant for change. Mental digression may be triggered by a briefly vibrating phone", explains Henning Beck, a neuroscientist from Frankfurt, Germany. In his book "To err is useful," he recommends actively ignoring the ringing cell phone while setting aside a pre-determined time during which to retrieve messages. "When we actively decide against the incoming stream of information, the thalamus in the midbrain, which is responsible for filtering all sensory input, will with time build resistance against distraction", says Beck. From a neurological perspective, however, distraction is not altogether bad, as short interruptions can also trigger inspiration as they help the brain pick up new ideas.

Emotion-driven knowledge acquisition

While the midbrain-based thalamus filters all sensory input, two long, curved structures, arranged in symmetrical order in both the right and the left hemispheres of our brains, constitute the true command center. The hippocampus connects the short-term memory with the long-term memory; if it is not intact, no new knowledge can be acquired. The beginning of each thought process is characterized by connections between individual cells that possess extensions, dendrites and axons, and are connected with up to 10,000 other cells. "Cells that fire together, wire together" is the term coined by Canadian psychologist Donald O. Hebb. Firing, in this instance, refers to the short electrical impulses that a nerve cell generates for the purpose of signal transfer.

"Highly complex processes such as learning and memory rely on a combination of very simple operations", explains Hannah Monyer, Head of Clinical Neurology at the German Cancer Research Center (DKFZ) and the University Clinic Heidelberg. Her research focuses on how our memory works and how we learn. Hannah Monyer, who co-authored the book "The Brilliant Mind" with the philosopher Martin Gessmann, states: "Learning happens through association. If different neurons, which are interconnected with each other, are stimulated at the same time, their connection will be reinforced by their simultaneous firing."

Don't forget to learn

Learning is initiated once features and objects continue to present themselves in the same fashion. Emotional aspects such as fear, reward or new experiences initiate the learning process, and newly acquired knowledge is subsequently stored in the cerebral cortex. During recall, the stored memory path is once again activated. The memory itself is then subject to adaptation to new impressions subsequently acquired. According to Monyer, the brain is less of a memory storage bank, but rather an "active organ of the future" that will influence our lives into old age. In order to keep the brain fit as long as possible, it is important to keep engaging in new activities and never to "forget to learn".

An occasional lapse of memory, however, is not merely a weakness of the brain, but rather "a clever trick which helps to select and newly combine the most important information from a thicket of impressions," explains Beck. Analog downtime and seemingly ineffective idleness are crucial for processing the flood of information. In fact, it is the apparent weaknesses of our brains, such as slips of the tongue and inadvertent mistakes that blaze the trail for innovative thought. In order to provide the best conditions for creativity, new ideas or learning, breaks are crucial. "The brain needs the opportunity to digest information. We must not begin to function at the level of the algorithm – computers will never take a break", emphasizes Beck. He believes that the big global ideas of the future will not be generated digitally but rather that they will be conceived in the analog format. "Computers follow rules, but we are in the position to break these rules. While a positive outcome may not always be certain, it is in fact these inaccuracies of thought that make us superior to artificial intelligence." ■

GOOD TO KNOW

From a neurological perspective, distraction is not automatically a bad thing. Short **interruptions may well lead to inspiration!**

Slips of the tongue or slips of the pen enable new **creative ways of thinking.**

Breaks are a crucial prerequisite for creativity, new ideas and learning.

Analog pauses and supposedly ineffective idleness help process the daily flood of information.