Genomic Psychiatry

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INNOVATORS & IDEAS: RISING STAR

Pierre-Eric Lutz: The role of epigenomic plasticity in the emergence and protracted course of psychiatric disorders

Pierre-Éric Lutz, a permanent researcher at France's CNRS (Centre National de la Recherche Scientifique) and Strasbourg's Institute of Cellular and Integrative Neuroscience, investigates epigenetic mechanisms underlying brain disorders such as addiction and depression. His lab employs genetic engineering in mice, high-throughput multiomics in mouse models and human cohorts, and bioinformatics. We are thrilled that in this Genomic Press Interview Dr Lutz shares insights into his life and career with our readers.

Part 1: Pierre-Éric Lutz – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I was born and raised in France, in a family in which being a medical doctor has long been the default option. As a teenager, I was primarily interested in playing video games, reading books, and listening to music. At the end of high school, I only had a vague idea of what I wanted to do with my life. Surprisingly enough, I ended up entering medical school. It took me a while to realize that my main interest was understanding disease's biological mechanisms. Therefore, I opted to take undergraduate courses in molecular biology and biostatistics in addition to medical training. Then, during my residency in general medicine, I completed internships in the psychiatry and neurology departments. This gave me the opportunity to work in a facility dedicated to the management of patients with severe addictions, who were notably receiving opioid substitution therapy. During these internships, I was deeply moved by the painful life histories of people affected by chronic psychiatric disorders. That is when I decided I wanted to understand how biological, socioeconomic, and cultural factors interact to trigger such profound maladaptive behaviors. In parallel to finishing my residency, I completed my basic science training with a Master's in neuroscience. Then, I engaged in a PhD, during which I worked in the laboratory of Professor Brigitte Kieffer at the Institute of Genetic and Molecular and Cellular Biology (IGBMC) and the University of Strasbourg, France. There, I got familiar with genetic manipulations and behavioral paradigms in the mouse, which we used to understand better how opioid receptors mediate the unmatched analgesic properties of opioids (drugs such as morphine or fentanyl) but also represent entry points to the development of substance use and anxiodepressive disorders.

We would like to know more about your career trajectory leading up to your current role. What defining moments channeled you toward this opportunity?

After obtaining my MD and PhD degrees in 2012, I had two significant objectives. First, because I had developed a strong interest in the emerging field of neuro-epigenetics, I was looking for a lab where I could get training in high-throughput sequencing approaches and related bioinformatic analyses. Second, I wanted to work in an environment with a robust clinical perspective oriented towards the biological understanding

Figure 1. Pierre-Éric Lutz, MD-PhD, Centre National de la Recherche Scientifique, France.

of behavioral deregulation. The laboratory of Professor Gustavo Turecki at the Douglas Research Center & McGill University in Montréal, Canada was the ideal place to achieve these two goals. I spent three years there, from 2013 to 2015, thanks to funding from the Fyssen Foundation, the Canadian Institutes of Health Research (CIHR), and the American Foundation for Suicide Prevention (AFSP). My projects focused on the role of epigenetic plasticity in the long-term consequences of childhood maltreatment, one of the strongest risk factors for psychopathology. The originality of our approach was that we conducted molecular analyses of human postmortem brains, available from the Douglas Bell Canada Brain Bank. This bank represents a unique resource as it collects and provides access to postmortem tissues and, importantly, also performs

Figure 2. The old city centre of Strasbourg, France, known as "Petite France," appears eerily quiet and deserted during the COVID-19 pandemic. The picturesque half-timbered houses and empty cobblestone streets along the canal are bathed in a soft, ethereal light, highlighting the historic architecture in the absence of the usual bustling crowds and vehicle traffic. This striking image taken by Pierre-Éric Lutz captures a surreal moment in time, showcasing the beauty and tranquility of the iconic neighbourhood under unprecedented circumstances.

psychological autopsies to retrospectively assess the demographic, clinical, and developmental histories of the donors. Our results notably provided evidence suggesting that childhood maltreatment may epigenetically reprogram critical brain physiological systems (opioid receptors) and cell types (oligodendrocytes) in the human brain. Following that postdoctoral experience, I returned to France in 2016 to join the laboratory of Drs Ipek Yalcin and Michel Barrot at the Institute of Cellular and Integrative Neuroscience in Strasbourg (figure 2). During this transition period and until 2018, I continued to work on the project that I had initiated in Montréal, while also participating in the projects of my host lab. In 2019, I was recruited as a permanent researcher by the French National Center for Scientific Research (CNRS), and I have since initiated my own line of investigation.

Please share with us what initially piqued your interest in your favorite research or professional focus area.
I have always been interested in trying to understand how the biological processes in the brain may underlie our behaviors and help explain why people feel sad or engage in dangerous or seemingly irrational behaviors. At the same time, during my medical studies, I developed a strong taste for genomics and molecular biology. Until recently, bridging the gap between these two epistemologically distant levels of analyses was difficult. This has changed with the advent of neuro-epigenetics. This young discipline seeks to decipher how complex behavioral traits may be mediated by changes in the conformation and functional properties of the genome. My interest in that type of research emerged during my post-doc years, as I used to sit next to bioinformaticians working at their computers. They would show me sequences of DNA or data from libraries I had generated from human brains, and we would try to identify genomic sites where, for example, changes in DNA methylation, a primary epigenetic substrate, may contribute to the dysregulation of genes and physiological processes involved in emotional regulation. In my lab, we now follow that framework. We try to leverage the power of the laboratory mouse, which allows us to mimic maladaptive behaviors in controlled experimental settings, with the investigation of human cohorts, using easily accessible peripheral tissues (such as blood), or postmortem brains (thanks to a continuous collaboration with Montréal).

What impact do you hope to achieve in your field by focusing on specific research topics?
I hope my work will represent a tiny contribution, among those of many others, to a better recognition of biological determinants of mental health. The objective is that this understanding may help decrease the stigma that is still strongly associated with psychiatric disease.

Please tell us more about your current scholarly focal points within your chosen field of science?
My lab is currently working on two main fronts. First, we refine the way we model addiction. To do so, we are currently developing a paradigm in which mice learn to express a voluntary behavior that triggers the delivery, directly into the brain, of a flash of light that, thanks to optogenetic tools, has reinforcing effects. With the repetition of this behavior progressively emerge compulsive-like responses that include resistance to punishment, aberrant motivation to get the reinforcing stimulus, or persistent response when it is no longer available. Because this model can be implemented relatively quickly in the mouse, it opens the door to targeted manipulations of the epigenetic machinery (for example, enzymes responsible for DNA methylation) to assess their role in the aforementioned complex behaviors. Second, like others, we are interested in improving the depth and resolution at which we measure and analyze epigenetic landscapes. Focusing primarily on DNA methylation, we are interested in using long-read sequencing and novel computational approaches to identify methylation patterns at the level of single reads, i.e., single alleles. The challenge we now face is to efficiently develop and combine these two lines of work that require a broad range of expertise, from experimental psychology to bioinformatics and computational biology.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
I have had the privilege to work during my PhD under the supervision of Professor Brigitte Kieffer (France) and my post-doc with Professor Gustavo Turecki (Canada). From Brigitte, I vividly remember the time and energy she was ready to devote to her trainees for one-on-one sessions. To Gustavo, I am grateful for the many opportunities I was given to develop as a scientist, with the liberty to pursue my intuitions and interests. I now try to reproduce these 2 aspects in my group.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?
I believe it is important that scientific research remains a domain where critical thinking, doubts, and humility are practical realities. Therefore, I am generally in favor of attitudes or initiatives that seek to minimize tendencies toward personalization, storytelling, or overstatements.

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What do you most enjoy in your capacity as an academic or research rising star?

I cherish the liberty I have to periodically decide on the focus of my research. I also enjoy the fact that I have to constantly evolve and learn new things to try to remain creative and productive.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

Outside of work, I spend most of my time with my wife and kids. We enjoy going to restaurants, seeing classic or funny movies, travelling, and doing many other things!

Part 2: Pierre-Éric Lutz – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Being perfectly happy seems like a dangerous idea.

What is your greatest fear?
Political extremism.

Which living person do you most admire?
I am a fan of people who dare to set their own path and are enthusiastic about what they do.

What is your greatest extravagance?
My average extravaganza level is relatively low, but I keep getting those remarks about my shoes.

What are you most proud of?
I try not to take pride in much of anything.

What is your greatest regret?
I wish I had learned to code earlier in my career.

What is the quality you most admire in people?
Humility.

What is the trait you most dislike in people?
Selfishness.

What do you consider the most overrated virtue?
Pride.

What is your favorite occupation (or activity)?
Reading the news.

Where would you most like to live?
Any place where the temperature never gets higher than 25°C / 77°F.

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[1] In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

What is your most treasured possession?
All those that are not material.

When and where were you happiest? And why were so happy then?
Every time I was confronted with a difficult concept, reading or set of experimental data, I had to slowly acquire and digest new knowledge in order to see the beginning of an understanding. There is fulfillment in these modest personal journeys.

What is your current state of mind?
I am worried about socioeconomic inequalities, climate change, political risk, and the world we are passing on to the next generation.

What is your most marked characteristic?
I try to remain objective and tempered.

Among your talents, which one(s) give(s) you a competitive edge?
I do not think I have any particular talent.

What do you consider your greatest achievement?
My two sons, obviously, a team effort with my significant other.

If you could change one thing about yourself, what would it be?
My communication skills.

What do you most value in your friends?
Kindness.

Who are your favorite writers?
Louis-Ferdinand Céline, Thomas Mann, and Julien Gracq.

Who are your heroes of fiction?
The Count of Monte Cristo.

Who are your heroes in real life?
Miles Davis.

What aphorism or motto best encapsulates your life philosophy?
Mourons pour des idées, d'accord, mais de mort lente (Georges Brassens).

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