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Michael Meaney: What is the biology that underlies the gene x environment interdependence that shapes brain health?

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As a distinguished James McGill Professor and now Professor Emeritus at McGill University, Michael Meaney's scientific journey is a testament to the power of curiosity in science. His fascination with how our environment shapes our genes, brain function, and mental health has led to discoveries that have changed how we think about human development. After leading groundbreaking research at McGill, he took his expertise to Singapore, where, as Director of the Translational Neuroscience program at ASTAR, he helped shape the innovative GUSTO birth cohort study. His profound impact on neuroscience is reflected not just in his impressive collection of honors – from the Order of Canada to his recent election to the American Academy of Arts and Sciences – but in how his work has touched lives. With over 650 publications to his name, Meaney has helped bridge the gap between molecular biology and public health. We are fortunate to have him share his insights with our readers in this Genomic Press Interview.

Figure 1. Michael Meaney, PhD, McGill University, Canada.

Part 1: Michael Meaney – Life and Career

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

As an undergraduate, I wandered aimlessly through the sciences and humanities, seeking some theme that might focus my studies. In a rare moment of insight, I reverted to my experience in high school, asking simply what subjects I found most interesting. The answer was Chemistry, Biology, and History. I think the central theme that drew me to these subjects was that each informed me about who we are and why we differ so greatly from one another.

I later enrolled in a course in Genetics, which in the 1970s was heavily focused on the central issues in developmental biology. The subject matter included discussions of embryology and pattern formation (i.e., the unfolding of the genetic 'blueprint') to understand the forces that make a frog, a frog, or a salamander, a salamander. At one point approached the Professor to express a greater interest in what makes one frog or salamander different from another. She responded sympathetically and suggested I take courses in Psychology.

From these courses (do note this was the 1970s), I found inspiration in the research of Harry Harlow, Seymore (Gig) Levine, and Victor Denenberg, showing that early experience could shape individual differences in the core physiological features of the stress response. I later found myself in the library with a book on the origins of cardiovascular disease. One compelling chapter spoke about the importance of stress, the effects of the biochemical signals activated by stressors on the circulatory system, and the resulting dangers, amongst others, of shear stress on the arterial walls. A greater stress response augured for poorer cardiovascular health. This science implied that early experience could influence the later risk for health outcomes. This conclusion was confirmed by the Harvard Stress Mastery study results, which showed that poor quality of early family life predicted the risk for early mortality – even amongst Harvard graduates. My path was established. I set out to understand the biological pathways by which early experience might shape neural development and later health outcomes.

A defining influence for my research was the conceptual brilliance of Donald Hebb of McGill. Hebb was the first to articulate the fundamental elements of neuroplasticity clearly and to create a framework for understanding the role of early experience on brain development and function. In doing so, he effectively disrobed the 'nature vs. nurture' emperor (Hebb was to nature vs. nurture what Edwin R. Murrow was to Senator Joseph McCarthy). The gene x environment theme thus emerged as the conceptual framework that has forever guided my science.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

My previous training in Child Clinical Psychology remains an inspiration. However, interventions targeting children and families in the 1970's were rather unsatisfying and rarely evidence-based. I decided instead to focus on the issues that brought me to this place, which (see above) concerned the mechanisms by which early experience influences neural development and brain health. The research was almost entirely focused on model organisms and neuronal cell cultures. We sought to understand the pathways by which early experience becomes embedded in brain function. Then, in 2002, The Canadian Institutes for Health Research created a major funding program to support translating findings from the basic sciences into programs focusing on child development and health outcomes using human cohorts. This seemed a unique opportunity to merge my basic science research with an ambition for clinical relevancy. I thus headed

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Figure 2. Michael Meaney (second from the right) enjoying dinner with colleagues from the Translational Neuroscience program in Singapore. The informal gathering at a restaurant decorated with beer-themed artwork, including an Estrella Galicia bottle illustration, represents one of their regular team dinners. These social gatherings reflect Dr. Meaney's commitment to mentorship and team building, which he cites as one of his most significant sources of professional satisfaction in his interview. The success of scientists and graduates from both Singapore and McGill teams has been particularly meaningful in his career.

a proposal, ultimately funded, to create the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) birth cohort study in Canada. This experience led to an invitation from the Agency for Science, Technology & Research in Singapore to establish a neurodevelopmental research program with a large and very well-funded longitudinal birth cohort study (Growing Up in Singapore Towards healthy Outcomes; GUSTO). I have served in this role for the past 17 years. This position, in turn, led to the creation of a Translational Neuroscience program that now includes multiple wonderful young and very independent principal investigators (PIs, see Figure 2). They are now leading the GUSTO studies on the origins of individual differences in brain health and, in doing so, creating a foothold for Biological Psychiatry in Singapore.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

I have always been genuinely fascinated by the search for the developmental origins of individual differences in brain development and function. More broadly, and inspired by Hebb, I bore a profound dissatisfaction with the conceptually flawed distinction between the influences of "nature" and "nurture". It seemed implausible that biology would operate along distinct, purely additive, and otherwise independent pathways to define phenotypic outcomes. This conceptual framework led to my focus on gene x environment interactions. Nevertheless, I was always curious about gene x environment interactions – what does the "x" mean? Thus, I derived my focus on environmental regulation of the epigenome and its effects on gene expression.

What impact do you hope to achieve in your field by focusing on specific research topics?

I fully expect the details of my research to fall by the wayside as a country road yields to a superhighway. However, the path, the themes, and the concepts might inspire subsequent generations. Who could hope for more?

Please tell us more about your current scholarly focal points within your chosen field of science.

I am enamored with applying novel computational approaches to 'big data' and, therefore, a renewed ability to address the issues at the core of my science. The large data sets of the day are an ideal playground for one seeking to document gene x environment interactions on health and well-being. The remarkable 'omics platforms and databases allow bioinformatic analyses to identify candidate biological pathways, including those that might underlie these gene x environment effects. It is a fantastic period for translational neuroscience.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

Intense visualization of individual data points seeking patterns often masked by the statistical analyses of group means or averages. I am also fond of reading older literature (and not simply because I am now part of it). Most importantly, I cherish the simple and admittedly frequent realization of being wrong. Growth as a scientist derives from the instances when the data sends you sulking back to the blackboard.

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?

We too readily embrace narratives and technology that appeal to the general public, achieve headlines, and attract venture capital, but are far too simplistic to capture the complex reality of brain health truly. I have, for example, watched as the extraordinary science of Selye, Cannon, Mason, Dallman, Stellar, McEwen, and de Kloet (amongst others) has been funneled into a now meaningless understanding of how we meet the

challenges of life. Whatever happened to Selye's brilliant distinction between stress and distress? Why have we villainized glucocorticoids? Try making it through an infection without them! I cringe at the thought of hordes of software developers and health gurus tripping over each other like drunkards at an open bar, inventing solutions to problems they do not understand.

To every problem, there is a solution that is simple, straightforward, and wrong.

What do you most enjoy in your capacity as an academic or research leader?
The mentorship of young scientists.

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?
Exploring the world's remote corners with my wife, whose capacity for truly unique insights never ceases to amaze me. Skiing a Black Diamond is a good second.

Part 2: Michael Meaney – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
I am blessed with many occasions of very real happiness, but I am poorly positioned to assess their perfection. They largely derive from family and science, but I would also note the simple joy of learning something new and meaningful.

What is your greatest fear?
Not rising to meet the challenges born from our recent science.

Which living person do you most admire?
Millions meet extreme adversity with courage, dignity, and persistence. Their heroic struggles exemplify the best of human nature. In their shadow, we can take some pride in being human.

What is your greatest extravagance?
Red wine, especially Italians.

What are you most proud of?
The success of so many graduates from our programs.

What is your greatest regret?
I wish I had stayed longer in my postdoctoral position in the McEwen lab at Rockefeller University. I still get misty-eyed whenever I walk through the gates at 66th.

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

What is the trait you most dislike in people?
Superficiality (i.e., insincerity).

What do you consider the most overrated virtue?
Humility. I should elaborate. I admire individuals who think and behave according to a realistic appreciation of their strengths and weaknesses, weighted realistically. Both confidence and humility should be a product of genuine self-awareness. Honestly, I find some charm in a little well-deserved arrogance. Which is a good thing considering the business I am in.

What is your favorite occupation (or activity)?
Biomedical research and all its moments. I remind our Fellows of how fortunate we are to work in a field that can break your heart, for this same deep connection allows us to occasionally soar.

Where would you most like to live?
I have always loved Montreal. I was born, raised, and lived most of my adult life, thriving in its vibrancy. I also like how its amusingly unstructured way of life embraces the variation so common across its inhabitants. We like different. But as I age, the south of Italy has considerable appeal. It is vibrant and charmingly unstructured, but warmer—and with better red wine. But Montreal is my home–another blessing.

What is your most treasured possession?
A BMWi328 M-package hard-top convertible – with *manual* transmission.

When and where were you happiest? And why were so happy then?
I have been blessed throughout my life, usually finding myself in the right place, doing the right things, and flourishing. I am now thoroughly enjoying the present; it embodies the joys of today and the aspirations of tomorrow.

What is your current state of mind?
Focused, no less ambitious but far more mindful, mostly as a function of age, experience, and occasional moments of insight. Aging bestows some remarkable gifts.

What is your most marked characteristic?
Talking/storytelling – probably to a fault. I am of Irish ancestry.

Among your talents, which one(s) give(s) you a competitive edge?
Breadth of expertise, which I owe to my mentors, and a fearlessness to explore new directions and methodologies. For whatever reason, I do not fear failure. That coupled with the willingness to embrace being wrong and a simple commitment to hard work.

What do you consider your greatest achievement?
Our research positioning environmental regulation of the epigenome and gene expression as a mechanism for gene x environment interactions, and its implications for the 'nature vs. nurture' controversy.

If you could change one thing about yourself, what would it be?
I wish I were more of a morning person. I love the earliest hours of the day as the sun rises, the evening mist clears, and everything seems possible.

What do you most value in your friends?
A sense of humor and the willingness to deploy it in any context.

Who are your favorite writers?
I have always been drawn to masterful storytellers – from Steinbeck's powerful social narratives to Barbara Tuchman's vivid historical accounts. Le Carré and Graham Greene have a special place in my heart for their sophisticated espionage tales, while Conrad's psychological depth never fails to move me. More recently, I have discovered Amor Towles, whose elegant prose has been an excellent addition to my literary world.

Who are your heroes of fiction?
Atticus Finch (To Kill a Mockingbird) and many others of this ilk.

[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.

Who are your heroes in real life?
Jane Stewart (Concordia University) and Bruce McEwen (The Rockefeller University). One could simply not envision more inspiring and generous mentorship.

What aphorism or motto best encapsulates your life philosophy?
Character is fate.

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