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Barbara Franke: Understanding the biological pathways from genes to altered behaviour in neurodevelopmental conditions like ADHD – paving the way for improved understanding and care in psychiatry

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In this Genomic Press Interview, Professor Barbara Franke, a trailblazing molecular psychiatrist at Radboud University in Nijmegen, shares her extraordinary scientific journey from an inquisitive child fascinated by nature to becoming one of the world's most influential researchers in biological psychiatry. With over 500 peer-reviewed publications and recognition among the top 1% most cited scientists globally, Franke has helped to revolutionize our understanding of the genetic foundations of neurodevelopmental disorders, particularly ADHD. Bringing together international experts for interdisciplinary research, she founded and leads multiple international research consortia, including the International Multicentre persistent ADHD Collaboration (IMpACT) and the ECNP Network ADHD across the lifespan. Her pioneering work extends beyond gene identification to illuminating the biological pathways from genetic variations to altered behaviour, employing innovative complementary approaches including bioinformatics, brain imaging genetics, and experimental models using fruit flies and human induced pluripotent stem cells. An elected member of the Royal Netherlands Academy of Arts and Sciences, decorated Knight in the Order of the Netherlands Lion, and recipient of numerous prestigious awards, Franke's scientific contributions are matched by her passionate commitment to international collaboration and mentorship of the next generation of researchers. Her recent move into epigenetics research, investigating the interplay between heritable and environmental influences on psychiatric conditions, illustrates her unwavering determination to contribute to a new nosology in psychiatry that will ultimately improve diagnosis, treatment, and management for millions worldwide. Guided by the German proverb "Die Suppe wird nicht so heiß gegessen, wie sie gekocht wird" ("The soup is not eaten as hot as it is cooked"), Franke's balanced approach to life and science continues to inspire groundbreaking advances at the intersection of genetics, neuroscience, and psychiatry.

Figure 1. Barbara Franke, PhD, Radboud University Medical Center & Donders Institute, The Netherlands.

Part 1: Barbara Franke – Life and Career

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

From my early childhood in Germany, I wanted to learn more about nature and biology. I was an inquisitive child, and animals in particular interested me. After briefly considering veterinary medicine while in high school, I studied Biology. I started my studies at the Justus Liebig University in Giessen, expecting to become a behavioural researcher studying the great apes in Africa. However, halfway through my curriculum's first part, I fell in love with molecular genetics during a practical session where we isolated DNA from HeLa cells. I thus switched universities, choosing one in the Netherlands, as my holiday love had turned into more (by now, we have been partners for 40 years). At Utrecht University, I discovered molecular signal transduction as the topic that fascinated me most, and I decided to do a PhD in this field. I helped unravel the regulation of the newly identified Rap1 protein, studying human blood platelets. Although

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I look back on a wonderful and inspiring time with important findings, I was drawn to science that was closer to a patient. I therefore took a postdoc position in the newly established Multifactorial Diseases Lab at the Human Genetics department of Radboudumc in Nijmegen.

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

In my first postdoc position, I worked on the genetic contributions to neural tube defects. Shortly after 2000, my department offered me a tenure-track position to develop a research line into the new topic of pharmacogenetics. However, after my head of department, Prof. Han Brunner, introduced me to Prof. Jan Buitelaar, who had become the head of Radboudumc's Psychiatry department, I knew that the aetiology of psychiatric conditions, and ADHD in particular, would become my research topic of choice. What attracted me most was the controversy around ADHD; people were still doubting the mere existence of this condition, especially in adults. There were many opportunities in the field of etiological research, and Jan Buitelaar was an excellent mentor. He opened up his network for me, and I could take part in the analysis of the first genome-wide association study (GWAS) of ADHD as part of the international IMAGE study in 2006.

We, and others working on various psychiatric disorders, very soon realized that our sample sizes would not be sufficient unless the whole field drew together. I became a founding member of the Psychiatric Genomics Consortium (PGC). Contributing to the gene-finding efforts of IMAGE and PGC, it had always been my main aim to do downstream research on the identified genes to understand the pathways leading from genes to altered behaviour and disease symptoms. I have been fortunate to be able to build my career in the area, developing a complementary suite of experimental approaches – in collaboration with colleagues – for this purpose; we use data-scientific bioinformatics and brain imaging genetics approaches as well as experimental approaches based on small animal models (especially the fruit fly *Drosophila melanogaster*) and human induced pluripotent stem cell-derived neural models.

I am absolutely amazed at how much we can already learn about the biological pathways and brain-cellular substrates underlying psychiatric conditions using data science methods and existing data, based on the infrastructures now publicly shared worldwide. However, I find experimental models indispensable, realizing that data-scientific models provide predictions and hypotheses based on statistics, which need experimental validation.

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

After I settled on my subject of psychiatric biological research, my career became relatively linear. I stayed at Radboudumc and became a founding member of the excellent, interdisciplinary Donders Institute for Brain, Cognition and Behaviour, which now brings together researchers from six centres across the Nijmegen campus. My research group flourished, and I was promoted to Associate Professor and later to Full Professor. I developed ambitions to contribute to strategy development in research and was entrusted with Theme leader roles in Donders Institute and Radboudumc over the years. In 2017, I was elected head of the Division of Genome Research at the Human Genetics department (with over 500 members) and served as a member of the department's management team. During my six years in this position, we redesigned our department's structure to strengthen our links with Maastricht University, which taught me invaluable lessons in change management. Armed with such knowledge, I additionally took the position as interim director of the Donders Institute in 2022-2023 and helped lead this institute into its new governmental structure.

In 2023, I was offered the position of head of the Cognitive Neuroscience department (now Medical Neuroscience) at Radboudumc. I now enjoy leading the team of almost 200 researchers at this cool and interdisciplinary department. I extremely cherish this position, which allows me to combine management with research again. An important lesson I have learned over the last five years is that the combination of research and management activities makes me most happy in my work.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

I changed fields after completing my PhD: I moved from cancer research to human genetics related to developmental diseases. This meant I had to rebuild my network from scratch, which took several years. Starting in psychiatric genetics/biology research, I also had to build a new track record. Such a move does not fit well with the requirements of the funding instruments available to support career development for postdocs and starting group leaders (i.e., personal grants). I had to look for other types of grant support and found them, e.g., in EU-funded international collaborative projects. I have enjoyed participating and leading several of those; it has been the most wonderful experience!

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

I do not know if the aspect I want to mention here really fits the term "habit" or "value", but I learned something about seizing opportunities during my career that I communicate to my research group and environment: Being a bit introvert and tending to over-think every one of my steps early in my career, I found myself missing out on several opportunities. At a certain point, I decided this would not happen again, and I changed tactics, my new motto being "jump first, think later". This has served me well over the years. I mentor my postdocs and young group leaders (especially the females) in this way – if after "jumping" you should find out that you really cannot do something you agreed to, there is always a way back; however, if you put thinking first, you will find that somebody else will already have jumped once you decide that something would be a good opportunity for you.

Another aspect worth mentioning is about being (too) busy: If you ask anyone in our field how they are doing, they will tell you they are busy, often mentioning stress. I did the same for a while. At a certain point, I appointed an excellent personal assistant, Marielle, who took a lot off my plate, and I had time at my hand for a while. I mentioned this to a wise colleague, who told me: "You will manage to fill up your own and your PA's agenda to the brim in no time, busy is just who you are". He was right, of course. I learned from this that I have a choice, and I choose to be busy; therefore, there is no reason to complain or be stressed. I am trying to convey this insight to group leaders around me, as it helped me get rid of my feeling of stress, at least reduce it.

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

Having changed departments, and with several of my former group members having become independent research group leaders, I have found myself in an excellent position to start a new line of research over the past 2-3 years. I have become intrigued by epigenetics, as it allows us to understand the interplay between heritable and environmental influences on psychiatric conditions. Time is finally ripe for such research in complex, multifactorial conditions like ADHD, now that we have tools and methods available to measure different types of epigenetic modifications and transcriptomes at single-cell resolution. We can, for example, use methods such as "villages in a dish" in iPSC-based human neural models to capture better the biological variability of genetic contributions to the phenotype of interest.

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

As a molecular biologist and basic scientist, I do have the ambition to contribute to improving diagnosis, treatment, and management of people with psychiatric conditions, ADHD in particular. I contribute to increasing our insight into the genes and biological mechanisms underlying those conditions and how we can employ such insights in the innovation of diagnostic tools, treatment, and prevention. Over time, I have become more ambitious. We still need a new nosology in psychiatry, and I want to

contribute to that by identifying genes and pathways. I realize there is a long way to go towards achieving such ambitions: we have just started to scratch the surface on genes and the biology of psychiatric conditions. Importantly, we still focus almost exclusively on risk and vulnerability, where resilience and protection can also be made tractable using genetics and molecular biological research.

What do you most enjoy in your capacity as an academic or research leader?
International collaboration and working as a team are very important ingredients for the pleasure I experience in my work. In addition, kindling the excitement of young people for molecular research and seeing my students/postdocs grow into independent, passionate researchers give me energy to continue my work.

At Genomic Press, we prioritize fostering research endeavours 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 you feel strongly devoted to?
The latter, yes: I strongly support integrating multiple disciplines into research, from the early design phase to the execution of a project. Still too often, we work in silo's, missing out on important input from other disciplines. In working towards understanding psychiatric aetiology, I am convinced that we need to involve researchers from different disciplines and other stakeholders – patients and/or their representatives, clinicians, teachers, employers, and also, e.g., industry and/or policy makers, where applicable. Too often, we lose momentum and/or findings end up in somebody's desk drawer rather than being translated into products for society. We need more efforts to prevent such things from happening.

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?
My work is my passion; it draws me in every day, if I let it. However, I also enjoy spending time with family and friends and doing sports very much. My partner and I moved out of the city a year ago into the village where he grew up. Although it means a substantially longer commute for me, we are delighted to have taken this step. We have spent substantial time decorating our new house and redeveloping our garden. Family and friends often come by now, and we always make time for them. It is a different lifestyle. I still spend time in the evenings and on weekends working, just because I love it.

Part 2: Barbara Franke – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
Being collaborative.

Among your talents, which one(s) give(s) you a competitive edge?
Being interested and able to integrate and translate insights across scientific disciplines.

If you could change one thing about yourself, what would it be?
I accept myself as I am, and I'm healthy and content, so I do not want to change anything.

What is your current state of mind?
I am well-balanced, and I generally have a content and positive state of mind. Professionally, I am incredibly excited and inspired by the current scientific possibilities in biological psychiatry.

What is your idea of perfect happiness?
Spending time with family and friends in nature in nice and warm weather.

When and where were you happiest? And why were so happy then?
One of my happiest moments was in June 2023, when I was standing on the terrace of a hotel room overlooking Ngorongoro Crater (see Fig. 2). It has been my greatest dream to visit Africa and see the wonderful nature and wildlife of Tanzania and Kenya. In 2023, when the world recovered from the coronavirus pandemic, I decided not to postpone any longer and made the trip.

What is your greatest fear?
My greatest fear is that war will come to Europe.

What is your greatest regret?
It is a waste of my time to think about regret.

What are you most proud of?
I am very proud that my relationship with my partner is now in its 40th year and still going strong.

What do you consider your greatest achievement?
I have already inspired several researchers from the next generation to continue and extend the research they started in my research group.

What or who is your greatest passion?
My work, my partner, and traveling in Africa.

What is your favourite occupation (or activity)?
Traveling and seeing new things, hiking in nature.

What is your greatest extravagance?
Travelling to faraway places.

What is your most treasured possession?
I tend not to bind myself to possessions, but I treasure things that remind me of happy times with family and friends. I love a photograph of my grandparents, for example, which shows them posing happily for me while working in their garden one summer.

Where would you most like to live?
I am happy where we live now, in a lively village close to beautiful forests. I would be even happier if my mother and sisters could live closer to us.

What is the quality you most admire in people?
Being able to shoot out right away, with well-argued responses, to every question put to them. I often need time to think before answering.

What is the trait you most dislike in people?
I dislike it when people behave as if they are better than others.

What do you consider the most overrated virtue?
If you consider virtues in their original sense, they cannot be overrated.

[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.

Figure 2. Barbara Franke, on the rim of Ngorongoro Crater in Tanzania, fulfilling her long-held dream of visiting Africa, which was a life-changing experience for her.

What do you most value in your friends?
Their ability to listen (and not only talk) so that we can sometimes be silent together without this being awkward.

Which living person do you most admire?
Among living persons, I admire Jane Goodall, now 91 years old, who has dedicated her life to the sustainable protection of chimpanzees and their habitats in collaboration with the local population.

Who are your heroes in real life?
I admire people who dedicate their lives to an important cause.

If you could have dinner with any historical figure, who would it be and why?
A dinner with Leonardo da Vinci would be fascinating, he was such a uniquely multi-talented person.

Who are your favourite writers?
Outside of work, I read for relaxation. I love English detective novels, such as Colin Dexter's Inspector Morse, Agatha Christie's Miss Marple, and Elizabeth George's Inspector Lynley.

Who are your heroes of fiction?
I do not think I have those.

What aphorism or motto best encapsulates your life philosophy?
"Die Suppe wird nicht so heiß gegessen, wie sie gekocht wird." This German proverb translates literally to "The soup is not eaten as hot as it is cooked." It means that things are often not as bad as they first appear or that situations often turn out less severe than initially feared.

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Barbara Franke[1]
[1]*Departments of Medical Neuroscience and Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Kapittelweg 29, 6525 EN Nijmegen, The Netherlands*
✉ *e-mail: Barbara.Franke@radboudumc.nl*