Genomic Press

Genomic Psychiatry

Advancing science from genes to society

Volume 1 | Number 5 | September 2025

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MARMO-AD
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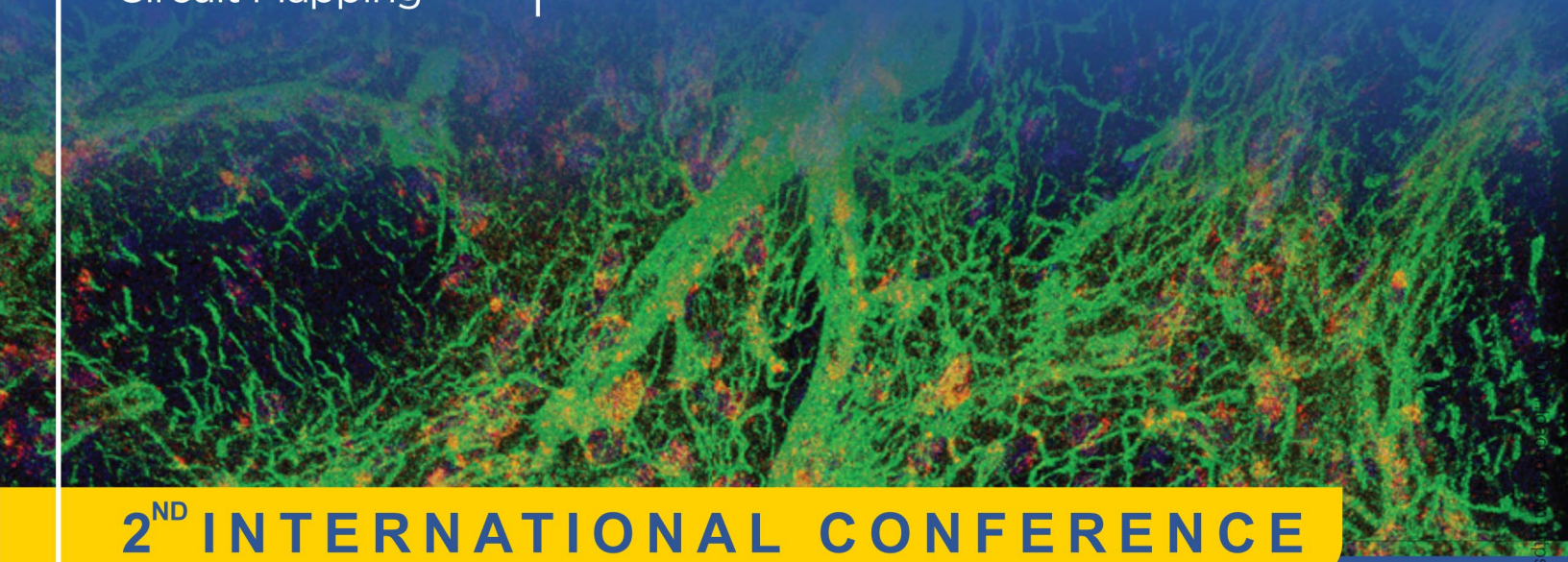

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Cover Art

Cover Image: Albrecht Dürer's "Melencolia I" (1514), a landmark of Renaissance engraving, reflects the complex inner world of melancholia through its symbolic landscape. The central, winged figure, often interpreted as the personification of melancholy, sits among the unused instruments of geometry and craft, visually echoing the theme of creative inertia and the psychological paralysis later described by Roubinovitch and Toulouse in their 1897 monograph (featured in this issue, pp. 21–29). Elements like the magic square, polyhedron, and scattered tools evoke the intact yet idle intellectual abilities typical of melancholic states, paralleling contemporary psychiatric views of preserved cognition amidst motivational impairment.

Dürer's composition, combining the body's languor, the intellect's stasis, and existential uncertainty (seen in the apocalyptic background), presages modern conceptions of depression as a multi-layered biopsychosocial phenomenon, connecting historical phenomenology to genomic research such as Serretti et al.'s study of C-reactive protein polygenic scores (pp. 30–35). Early impressions of this engraving, pulled from Dürer's original copper plate, are held by major museums worldwide, including the Metropolitan Museum of Art (New York), the British Museum (London), the Albertina (Vienna), the National Gallery of Art (Washington, D.C.), and the Museum of Fine Arts (Budapest). Image source: Public domain.

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EDITORIAL

From melancholia to molecular mechanisms: Bridging centuries of understanding depression

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Two articles in the current issue of *Genomic Psychiatry* present an interesting story spanning over a century of mental health research. Kendler and Justis carefully translate and analyze the 1897 monograph "La Mélancolie" by Roubinovitch and Toulouse (1). Meanwhile, Serretti et al. employ polygenic score analysis, showing that the genetic liability for C-reactive protein (CRP) associates with depression phenotypes and treatment outcomes (2). This gap in time, from 19th-century phenomenology to 21st-century genomics, illustrates the significant progress made in psychiatric science and the enduring relevance of specific clinical observations.

The extraordinary contribution by Kendler and Justis extends far beyond historical commentary. Their meticulous English translation of over 270 pages from the original French text, covering the first four chapters and part of the fifth, makes this seminal work accessible to the Anglophone scientific community for the first time. This translation, available as Open Access supplementary material in this issue of *Genomic Psychiatry*, reveals the extraordinary depth of clinical observation in the original monograph. Roubinovitch and Toulouse documented 22 detailed case histories and provided comprehensive coverage of symptoms, signs, subtypes, illness course, and outcomes with a thoroughness that rivals modern clinical texts. Their vivid descriptions, from the 'vertical folds formed immediately above the root of the nose' to patients who 'pull their fingers, tear their hair, scratch their forehead,' demonstrate a level of phenomenological precision that modern psychiatry, with its emphasis on biological markers and standardized assessments, sometimes risks losing. The availability of this translation allows contemporary researchers to engage directly with these historical observations and appreciate how remarkably consistent the core features of melancholia have remained across 127 years.

The persistence of phenomenology

What strikes the contemporary reader most forcefully about the observations of Roubinovitch and Toulouse is their remarkable clinical acuity. It is reflective of what we now call major depressive disorder, as described as "pain, slowed-down mental functions". Their awareness of the "psychophysical decrease", which saw an almost complete slowing down of thought and motor-power, foreshadows what we call psychomotor retardation. Their contemplation of the somatic consequences of melancholia is perhaps the most prescient. This takes the form of a change in 'coenesthesia' (body feeling). It produced 'a distressing affective tone'.

Serretti and his colleagues shared data that has an interesting connection to this body focus. The CRP polygenic scores' association with body mass index, appetite changes, and metabolic features suggests that careful observations of the body-mind interface in melancholia have captured something essential about the phenomenology of depression. What alienists of the nineteenth century inferred from meticulous clinical observation, we now attribute to specific genetic architectures that influence inflammatory pathways.

The striking consistency of psychiatric syndromes across centuries raises a fundamental question: Are we discovering biological mechanisms that explain timeless clinical phenomena, or do the observations of our predecessors inevitably shape our biological investigations? While biological systems constrain the possible forms of mental illness, cultural and clinical traditions determine how we perceive and classify these manifestations.

From psychalgia to polygenic scores

As research has developed over the past thirty years, the concept of melancholia has shifted from "psychalgia" (mental pain) towards a view of immune-metabolic depression subtypes (3). We no longer think about mental suffering in the same way. The psychalgia framework of the nineteenth century asserted that melancholic patients were hypersensitive like neuralgics, experiencing exquisite mental pain from normal psychological stimuli. While there may not be molecular specificity to this psychophysiological model, it captures a vital truth about depression. Depression involves altered processing of both internal and external stimuli.

Serretti and colleagues' findings offer a molecular basis for the mentioned clinical observations. The authors found that those with a genetic liability to C-reactive protein (CRP) have certain depressive features, such as changes in appetite and metabolic dysregulation. An intriguing possibility is then raised: Could the "distressing emotional tone" described by Roubinovitch and Toulouse be inflammatory in nature? The relationship between CRP-PGS and treatment response follows a U-shaped distribution: genetic liability for CRP is highest in treatment-resistant patients, intermediate in responders, and lowest in non-responders, suggesting that distinct biological mechanisms may underlie what clinically appears to be a single depressive syndrome.

This complexity goes beyond a straightforward linear correlation between inflammation and mood. The hypothesis of depression as an inflammatory disorder has evolved from an early observation of sickness behaviour to a sophisticated model linking metabolic, neuroendocrine, and neurotransmitter systems. Serretti et al.'s finding of a U-shaped relationship linking treatment response to genetic liability for CRP suggests that the role of inflammation in depression may be context-dependent, being beneficial at certain levels or in specific individuals and pathological in others. This sophisticated viewpoint coincides with newer ideas regarding inflammation in psychiatric illnesses, which is needed for normal responses to stress but can be harmful if it goes wrong.

We chose Albrecht Dürer's "Melencolia I" (1514) for this issue's cover in order to provide a visual bridge between these two temporal perspectives. This Renaissance masterwork depicts a winged figure surrounded by unused tools and instruments, embodying the paralysis of will and creative stagnation that would later be termed "psychophysical decrease." The engraving captures, with remarkable prescience, the phenomenology that Roubinovitch and Toulouse would describe nearly four centuries later: the intact but unutilized intellectual capacities, the dejected

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posture signaling both physical and mental exhaustion, and the pervasive sense of futility despite available resources. That a 16th-century artist could so accurately render the clinical features of melancholia underscores the transcultural and transhistorical nature of this condition, even as our understanding of its biological underpinnings continues to evolve.

The challenge of heterogeneity

Both pieces work through the infamous variability of depression. Roubinovitch and Toulouse wondered whether melancholia was a morbid entity or a heterogeneous compound of physical and psychic problems which no natural link unites; final acceptance of the probable fact that psychiatric categories are probably only provisional symptomatic groupings which will one day be transformed into more exact conceptions of the nature of the relationships which unite the facts.

This provisional nature persists. Despite progress in genomics, neuroimaging, and molecular psychiatry, depression is still syndromically diagnosed. Serretti et al. propose the identification of an immunometabolic subtype, which is undoubtedly a step towards the "approximately exact conceptions" vocabulary, but only explains 1.9% of variance in treatment outcome. This serves as a humbling reminder that there are biological reasons for depression.

The heterogeneity issue significantly impacts our understanding of psychiatric classification. The RDoC initiative focuses on data from multiple areas to help create a comprehensive description of behavior. However, the articles in this issue demonstrate how clinical syndromes, although imperfect, still capture meaningful patterns of suffering. Phenomenological descriptions by Roubinovitch and Toulouse, with their emphasis on resignation, derealization, and the lived experience of melancholia, suggest that a strictly biological approach is likely to miss clinically relevant data. Dialectical thinking that we preserve phenomenology while advancing biology seems the way ahead.

Environmental and developmental considerations

Neither article exists in an environmental vacuum. Roubinovitch and Toulouse say melancholia requires the absence of "sufficient reason" – it is not an understandable reaction to not winning something or to loss. The said distinction foreshadows controversies concerning bereavement exclusions and adjustment disorders, suggesting that psychiatric diagnosis has always struggled with the threshold of normal and pathological concerning life events.

The research by Serretti et al. suggests that CRP genetic liability is associated with lower employment status, which raises questions about gene-environment correlations and the social determinants of health. Does being genetically prone to inflammation make people more vulnerable to social adversity? Or does social disadvantage activate inflammation in genetically susceptible people?

The bidirectional relationships between biological vulnerability and environmental stress complicate simple genetic determinism, reminding us that even highly heritable traits manifest in social settings. These gene-environment interactions may have particularly grave consequences when inflammatory liability intersects with social adversity. The inflammatory cascade triggered by such interactions could contribute to the most severe manifestations of depression, including suicidality.

Indeed, previous work has shown that polygenic risk scores (PRS) for neuropsychiatric, inflammatory, and cardio-metabolic traits highlight possible genetic overlap with suicide attempt and treatment-emergent suicidal ideation. Specifically, the association between loneliness-PRS and suicide attempt is consistent with previous strong evidence supporting the relevance of this trait on suicide risk (4). This suggests that the same inflammatory pathways linking CRP genetic liability to depression phenotypes may, under conditions of social isolation or disadvantage, contribute to life-threatening outcomes.

Implications for precision psychiatry

The polygenic studies already show such modest effect sizes that many people take little notice. Those modest effect sizes should be viewed in the context of the numerous and perhaps more severe problems in psychiatry. Unlike the infectious diseases whose progress in microscopic and bacteriological analysis was enviously noted by Roubinovitch and Toulouse, psychiatric disorders are the result of thousands of genetic variants interacting with environmental exposures throughout development. The fact that CRP-PGS captures a share of variance not accounted for by clinical predictors suggests that we are uncovering genuinely novel biological information, even if it does not significantly improve prediction.

The way ahead requires integrating various levels of analysis from physical, chemical, and emotional environmental exposures to imaging, genomic, metabolic, endocrine, and immune contributions to psychopathology (5–8).

Digital phenotyping and ecological momentary assessment developments provide a novel toolset for capturing the temporal dynamics of depressive states that Roubinovitch and Toulouse could observe only cross-sectionally (9). These technologies could help us understand how genetic liabilities lead to momentary experiences of suffering. That might open up intervention points that are invisible to other, more traditional assessment methods.

The enduring value of historical perspective

Perusing the 1897 monograph of Roubinovitch and Toulouse would be more than mere historical curiosity. Clinical value exists in their phenomenological insights, emphasis on resignation, distinction between reactive sadness and true melancholia, as well as attention to lived experience and derealization. This reminds us that while we are extracting molecular mechanisms, one should not lose sight of the subjective experience of mental suffering, which is the domain of psychiatry.

Also, today's researchers can take a cue from their humility. By recognizing that psychiatric categories are provisional, theorizing mechanisms with uncertainty, and employing different observational strategies, they demonstrate the kind of pluralistic thinking we need to move our field forward.

Looking forward

As we position ourselves within genomic discovery and phenomenological tradition, several priorities come to mind. First, we need better integration of genetic findings with clinical phenomenology. Serretti et al.'s data indicate a correlation between CRP genetic liability and specific symptoms. This suggests careful phenotyping continues to be essential even in the genomic era. Additionally, we need to develop effective therapies that consider biological heterogeneity and can be effectively implemented clinically. A non-linear relationship between CRP-PGS and treatment response suggests complex therapeutic implications that require further investigation.

Furthermore, new insights into immunometabolic subtypes may help us develop novel predictors of outcomes, leading to potential new treatment options (10). Could anti-inflammatory therapies be particularly beneficial for any subset of depressed patients with genetically driven inflammatory dysregulation? Early evidence is conflicting regarding the use of inflammatory biomarkers for treatment selection, but genetic data suggest that this approach would be a worthwhile endeavor with more sophisticated stratification.

Ultimately, the answer to our opening question—whether we are discovering mechanisms that explain timeless phenomena or are shaped by our predecessors' observations—appears to be both. The CRP genetic findings validate what Roubinovitch and Toulouse observed about the "distressing affective tone" and somatic manifestations of melancholia, suggesting that careful clinical observation can indeed capture biological truths that await molecular discovery. However, our decision to investigate inflammatory pathways in depression was simultaneously guided by centuries of phenomenological descriptions emphasizing the body-mind interface.

We are not simply uncovering pre-existing biological facts, nor are we merely prisoners of historical frameworks. Instead, we exist in a dialectical relationship with our intellectual heritage: the phenomenology of the past directs our biological investigations, while our molecular findings retrospectively illuminate and validate historical observations. Similar to how the "symptomatic groupings" of Roubinovitch and Toulouse

became our diagnostic categories, our current categories—and even our polygenic scores—are likely to be modified by future discoveries.

The journey from melancholia to molecular mechanisms continues, not as a linear progression from ignorance to truth, but as a spiral where each generation's observations both constrain and enable the next. In bridging these perspectives, we honor the humanistic traditions of psychiatry while embracing its scientific future. The conversation between past and present, exemplified in this issue, enriches our understanding and points toward a psychiatry that is both more scientifically grounded and more deeply human.

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INNOVATORS & IDEAS: RISING STAR

Mateus Vidigal de Castro: Cellular and genetic determinants of healthy aging and disease resilience

Genomic Psychiatry September 2025;1(5):4–6; doi: https://doi.org/10.61373/gp025k.0068

Keywords: Aging, longevity, resilience, stem cells, genetic diversity, progeria

Dr. Mateus Vidigal de Castro is a postdoctoral researcher at the University of São Paulo, Brazil. His research focuses on the cellular and molecular mechanisms underlying healthy aging, disease resilience, and extreme longevity. He leads studies involving induced pluripotent stem cells (iPSCs) derived from centenarians, aiming to better understand the biology of aging and its intersection with infectious diseases such as COVID-19. Dr. de Castro is also a member of Sigma Xi, the Scientific Research Honor Society. He is particularly passionate about exploring how genetic diversity in underrepresented populations can reveal novel insights into longevity and human health. In this Genomic Press Interview, Dr. de Castro shares with our readers his reflections on his life, career, and the scientific journey that continues to inspire him.

Part 1: Mateus Vidigal de Castro – Life and Career

Where were you born, and where do you live now?

I was born in Campinas, a city about one hour's drive from São Paulo. Because of my work, I currently live in São Paulo, the largest city by population in the Americas, the Western Hemisphere, and the Southern Hemisphere.

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

I grew up surrounded by science. Both of my parents were researchers, and from an early age, I was fascinated by the invisible world—the world beyond what the eyes can see. Watching my parents' dedication to research shaped my values and sparked my curiosity about biology and how life works at the cellular level. My real passion for science was ignited when I first looked through a microscope during college. Seeing living cells for the first time was a life-changing experience—I knew I wanted to dedicate my life to understanding the mechanisms of life that are hidden from the naked eye. My academic journey was not always easy. I faced many rejections when applying for my first research opportunity. However, persistence paid off. I eventually joined a neuroscience lab, where I learned advanced microscopy techniques and published my first papers. That experience solidified my passion for research. Later, I had the opportunity to join one of Brazil's leading genetics research centers under the supervision of Professor Mayana Zatz, which opened the door for me to work in the fields of human genetics, aging, and longevity. Since then, my mission has been to use science to understand better why some people live exceptionally long and healthy lives and how we can translate that knowledge to improve human health.

Figure 1. Mateus Vidigal de Castro, PhD, University of São Paulo, Brazil.

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

I have always been fascinated by Brazilian supercentenarians—those individuals who have lived to be over 110 years old—and this has fueled my interest in studying the genetics behind exceptional longevity.

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

The pandemic forced me to completely revise my research project, as social distancing made it impossible to collect blood samples from volunteers in their homes. At that moment, we decided to study centenarians who recovered from COVID-19 as a model of resilience. That was the turning point that sparked my focus on longevity research.

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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 did not undertake any research internships abroad during my PhD or postdoctoral studies, and I sometimes regret not having had that international experience. However, staying ended up being a transformative decision. I had many unique opportunities and played a leading role in significant research projects at my center, which significantly shaped my career.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
Although I consider myself a competitive person, I take my ethical principles very seriously. For me, my efforts are always in service of science, not personal ambition. I firmly believe that scientific progress must be built on integrity, respect, and collaboration. I highly value the opinions and perspectives of my current supervisor and colleagues, and I strive to create an environment where open dialogue and mutual respect are prioritized.

Please tell us more about your current scholarly focal points within your chosen field of science.
My current research focuses on understanding the biological mechanisms that drive healthy aging, disease resilience, and extreme longevity. My goal is to investigate how genetics, cellular mechanisms, and immune responses contribute to exceptional longevity and resistance to infectious diseases such as COVID-19. I also have a strong personal interest in rare progeroid syndromes and in studying rare populations in general.

What impact do you hope to achieve in your field by focusing on specific research topics?
I hope to discover something that contributes to promoting human health—whether through the development of new treatments, improved diagnostics, or strategies to prevent age-related diseases.

What do you most enjoy in your capacity as an academic or research rising star?
I love the creative side of science—designing experiments, solving problems, and thinking about how to connect molecular mechanisms to real-world health outcomes. I also deeply enjoy mentoring students, collaborating with colleagues, and being part of a global scientific community that shares the same passion for advancing knowledge.

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 you feel strongly devoted to?
Brazil is a country of huge inequalities, and this inevitably impacts science. Research is often undervalued, underfunded, and underprioritized. There are very few resources, few women in leadership positions, and a limited number of Black scientists represented in academia. The lack of diversity and representation across multiple layers of society truly frustrates me. As an openly homosexual scientist, I feel a strong personal responsibility to help bring more visibility to underrepresented groups in science. I believe that diversity—whether it is cultural, racial, gender, or sexual orientation—is not just a matter of fairness but a driver of better, more innovative science.

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 enjoy spending time with my family and close friends. I love traveling and exploring new places. I also enjoy quiet moments. Spirituality is an important part of my life as well; I often find peace in prayer and moments of reflection. I want to spend more time close to nature.

Figure 2. Mateus and his nephew Nicholas visiting the iconic statue of Christ the Redeemer in Rio de Janeiro, Brazil. They enjoy spending time together and traveling whenever they can, preferably to beach destinations.

Part 2: Mateus Vidigal de Castro – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
Kindness and generosity are my most defining traits.

Among your talents, which one(s) give(s) you a competitive edge?
Creativity is one of my biggest strengths. I also tend to perform very well under pressure — sometimes too well, I think. (laughs).

If you could change one thing about yourself, what would it be?
Sometimes, I make things more complicated for myself by taking on too many commitments, even when I know I probably will not have enough

[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.

time for everything. I am still learning to set healthier boundaries and say no when necessary.

What is your current state of mind?
My current state of mind is a mix of gratitude, determination, and reflection. I am grateful for everything I have accomplished so far, and I am determined to continue pushing forward with my research and projects while also being reflective on how to balance work, life, and my well-being.

What is your idea of perfect happiness?
For me, perfect happiness is feeling at peace with myself and knowing that my life and work have meaning and a positive impact on others."

When and where were you happiest? And why were you so happy then?
I was probably happiest when I was accepted for my postdoctoral position at the University of São Paulo. But beyond professional milestones, I am also thrilled in the simple moments — being with my family and close friends or in moments of spiritual connection.

What is your greatest fear?
I have many fears, but my greatest ones are related to violence.

What is your greatest regret?
My greatest regret is not having completed an international research internship during my PhD or postdoctoral studies. Sometimes, I feel that I missed the opportunity to experience a different academic culture and expand my network further. However, at the same time, staying allowed me to take the lead on important projects and grow significantly as a scientist.

What are you most proud of?
I am most proud of the personal and professional efforts I have made over the past few years.

What do you consider your greatest achievement?
To date, my most notable achievement has been consistently delivering meaningful and solid work throughout the COVID-19 pandemic. It was a tough time — I lost some people very close to me, and it was emotionally devastating. Still, despite the personal pain and all the uncertainties, I managed to conduct my postdoctoral research with dedication.

What or who is your greatest passion?
My greatest passion is science. Moreover, as a person, it is my father (in memoriam) who was my biggest inspiration and taught me the values I carry today.

What is your favorite occupation (or activity)?
I enjoy reading about the history of the Catholic Church and related topics. Catholicism fascinates me — not only from a spiritual perspective but also from a historical and cultural one.

What is your greatest extravagance?
Shopping. If I could, I would go to the mall all the time! (laughs).

What is your most treasured possession?
I could say my house or my car, but honestly, my most treasured possessions are my Catholic relics!

Where would you most like to live?
I loved living in São Paulo, Brazil, before I moved here, but I have to admit that I miss my hometown, Campinas.

What is the quality you most admire in people?
Kindness. I admire people who are kind, empathetic, and respectful to others.

What is the trait you most dislike in people?
I dislike when people are rude, disrespectful, or impolite. It is something I cannot stand.

What do you consider the most overrated virtue?
Perhaps blind obedience. It is essential to respect rules but also to question them when they do not make sense or when they harm individuals.

What do you most value in your friends?
I value their support, their presence, and the time they choose to share with me.

Which living person do you most admire?
My sister. She is an incredible woman. She always gets whatever she wants! (laughs).

Who are your heroes in real life?
My father. He was my father, mother, and friend — all in one. He is my greatest hero in life.

If you could have dinner with any historical figure, who would it be and why?
It would be Rosalind Franklin. I would love to hear her version of the DNA discovery — a story that history did not tell fairly. She is one of my greatest inspirations in science, along with Marie Curie. Honestly, having dinner with both of them together would be an absolute dream.

Who are your favorite writers?
Clarice Lispector, a Brazilian writer. I admire her depth, sensitivity, and reflections on life and identity.

Who are your heroes of fiction?
Batman.

What aphorism or motto best encapsulates your life philosophy?
"If you believe, you can achieve."

São Paulo, São Paulo, Brazil
22 June 2025

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Genomic Psychiatry

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INNOVATORS & IDEAS: RESEARCH LEADER

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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Keywords: Neurodevelopmental disorders, ADHD across the lifespan, genetics, molecular biology, biological pathways

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.

Nijmegen, The Netherlands
27 April 2025

Barbara Franke[1]
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Genomic Psychiatry

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INNOVATORS & IDEAS: RESEARCH LEADER

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

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Keywords: Epigenetics, gene-environment interaction, neurodevelopment, translational neuroscience, early-life experience, brain health

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.

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.

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

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.

Montréal (Vérdun), Québec, Canada
13 December 2024

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INNOVATORS & IDEAS: RESEARCH LEADER

Peter Falkai: In order to understand the neurobiological origins of psychoses we need to understand the genetic underpinnings of brain plasticity and its modulation due to environmental risk factors

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Keywords: Neurobiology of psychotic disorders, schizophrenia, brain structure, happiness, family

Peter Falkai stands as one of the world's leading authorities in psychiatric research, particularly in understanding the neurobiology of schizophrenia. As a Scientific Member of the Max Planck Society and Director and Head of the Hospital at the Max Planck Institute of Psychiatry since October 2024, he continues to advance our understanding of mental health disorders. His distinguished career spans over three decades, during which he has held multiple prestigious leadership positions, including President of the European Psychiatric Association (2021–2023) and current President of the World Federation of Societies of Biological Psychiatry. A member of the German Academy of Sciences Leopoldina, where he served as Senator of the Neurosciences Section, Prof. Falkai has been instrumental in shaping modern psychiatric research and treatment approaches. His groundbreaking work on brain plasticity and innovative treatment combinations has opened new pathways for understanding and treating psychotic disorders. As site spokesperson for the German Centre for Mental Health and former President of the German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology, he continues to bridge the gap between basic research and clinical application. In this Genomic Press Interview, Prof. Falkai graciously shares insights into his remarkable professional journey and personal life, offering readers a glimpse into the mind of one of psychiatry's most influential figures.

Figure 1. Peter Falkai, MD, PhD, Munich University Hospital, Germany.

Part 1: Peter Falkai – 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 a first-year medical student when I listened to the lecture on human neuroanatomy and was immediately taken by the topic of "brain structure and functioning." After one of the subsequent lectures, I asked the professor to recommend a seminar to deepen my knowledge of this subject. I attended the suggested one and had to do a seminar work on Parkinsons' disease, on which topic I read many papers without – at least so it felt – understanding any of them. However, the paper I handed in was well received. I went back to the professor of neuroanatomy, who was also the director of the C. and O. Vogt Institute of Brain Research at that time, and asked whether I could join a research group. He introduced me to Bernhard Bogerts, who opened my passion for mental disorders, especially schizophrenia.

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?

Bernhard Bogerts supervised my M.D thesis and enabled me to spend 4 months at Tim Crow's group at his CRC unit in London in 1987, which was and still is a model for how basic and clinical researchers can interact and achieve meaningful research. I then followed Bernhard to the Department of Psychiatry at the Heinrich-Heine University in Düsseldorf, where I assisted him build up a neurohistological laboratory besides doing my specialization in psychiatry. As a clinical psychiatrist, I was influenced by my first chair, Prof. Heinrich, and in terms of clinical leadership by his successor, Professor Gaebel. In 1996, I moved on to the Department of Psychiatry of the University of Bonn, headed by Prof. W. Maier, where I enjoyed learning much about the genetics of mental disorders and how to build international networks and collaborations. In 2002, I obtained my first chairperson position in Homburg/Saar and Göttingen. These stations prepared me to take up my current and most relevant leadership role as the head of the Department of Psychiatry at the Ludwig-Maximilians-University in Munich, formerly led by Emil Kraepelin (1902–1924). This year, I was appointed director of the Max-Planck Society and head of the Department of Psychiatry at the Max-Planck Institute of Psychiatry. Bridging these two institutions allows for bringing together excellent basic and clinical research.

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

I was stunned during my work with Bernhard Bogerts by how unremarkable the Nissl-stained sections of patients with schizophrenia looked under the microscope in comparison to sections of Patients with late-stage Alzheimer's or Parkinson's disease. This was in sharp contrast to the medical records of the patients with schizophrenia, who were ill for a long time

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and demonstrated a marked functional decline as the consequence of illness. Fostered by Jan Stevens, we performed a Holzer stain per case to see whether a significant degree of gliosis could be detected, which was not the case. We then quantified astroglia using GFAP, and neither found any differences, refuting the idea of schizophrenia being a degenerative disorder. Since then, I have been convinced that schizophrenia is a disorder of disturbed regeneration, which was supported when we found that aerobic exercise recovers the hippocampal volume loss, reduces negative symptoms, and improves cognitive dysfunction in this disorder.

What impact do you hope to achieve in your field by focusing on specific research topics?
20 years ago, I started to become interested in the question of what aerobic exercise induces in the brains of patients with schizophrenia. To our surprise, our research group could develop several lines of evidence from post-mortem, imaging genetics, and induced pluripotent stem cell (iPSC) studies, which point to myelin-based plasticity and the involvement of the synaptic machinery. We initiated an RCT where we combined aerobic exercise and the repurposed drug Clemastine to see whether this has a bigger and longer-lasting effect on myelin regeneration, leading to improved cognition. If this were true, it would open the door for more repurposed or new targets to improve neural plasticity in schizophrenia, leading to improved treatment options, especially in the early phases of the illness.

Please tell us more about your current scholarly focal points within your chosen field of science.
I do believe that only by understanding the mechanisms of mental disorders we will be able to conceptualize mechanistically informed new treatments, which will lead to progress in psychiatry. Therefore, I hope that with our current work on disturbed myelin plasticity in schizophrenia, we can find mechanistic understanding in this small area, which eventually should result in targeted treatments, at least in a subgroup of patients.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
I enjoy getting up early, doing my routine jobs, and then start reading the research articles I had picked up the days before. I continue to do so late in the evening when most people rest, but when I enjoy thinking and dreaming about current and potential future research projects. I enjoy it when our young people talk about their science, and I regard it as a privilege to read their papers and watch how they develop. I love to listen to good talks and, therefore, attend some lectures every year on topics with which I am not very familiar.

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?
Following the 1956 Hungarian Revolution, my family and many relatives settled across Europe and beyond. Since then, English has been our common language at family gatherings because we have built lives in different countries. Therefore, I enjoy different views and ideas from different cultures. I can also understand the fears such multicultural communities can mean to some people, but based on my experiences, fostering research endeavors based solely on their inherent merit is a sound basis for excellent research.

What do you most enjoy in your capacity as an academic or research leader?
To listen and interact with scientists in our department and beyond and exchange new research ideas and methods.

Figure 2. Peter Falkai (center) preparing for the Tegernsee-Lauf, a scenic half-marathon around Lake Tegernsee in Bavaria, with his son (left) and Professor Jens Werner, Chair of Surgery at Ludwig-Maximilians-University Munich (right). The Tegernsee-Lauf is one of Germany's most picturesque running events, taking place in the Alpine foothills about 50 km south of Munich.

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 my professional confines, I most enjoy spending time with my family and friends. Since I love travelling very much, my biggest joy is traveling to unknown places with them. I also enjoy spending time on my own, reading, and running. Every weekend, I run approximately 20 kilometers with our dog, 10 km on Saturday and 10 on Sunday, always early in the morning.

Part 2: Peter Falkai – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Spending time with my family and/or friends.

What is your greatest fear?
To lose a close family member.

Which living person do you most admire?
Eric Kandel.

[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 greatest extravagance?
To travel to amazing places.

What are you most proud of?
That I became a member of the German Academy of Science (Leopoldina).

What is your greatest regret?
That I did not spend more time abroad visiting top research groups as a junior person before entering the clinic.

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

What is the quality you most dislike in people?
Not being able to listen to other people.

What do you consider the most overrated virtue?
Being orderly.

What is your favorite occupation (or activity)?
Reading, listening, and talking to people.

Where would you most like to live?
Munich.

What is your most treasured possession?
My wife and kids.

When and where were you happiest? And why were you so happy then?
I am happy now, but I was even happier when the kids were still living with us, and we discussed future plans and ideas.

What is your current state of mind?
I am happy and content with my life as it is now.

What is your most marked characteristic?
Being disciplined.

Among your talents, which one(s) give(s) you a competitive edge?
Ambition.

What do you consider your greatest achievement?
To become a Department Chairperson in Munich.

If you could change one thing about yourself, what would it be?
Be more patient.

What do you most value in your friends?
A sharp mind and a big heart.

Who are your favorite writers?
Thomas Mann, Svetlana Alexievich, and Ferdinand von Schirach.

Who are your heroes of fiction?
People who under difficult conditions find their way and are successful.

Who are your heroes in real life?
Parents with small kids who do their jobs (e.g., research) with much passion

What aphorism or motto best encapsulates your life philosophy?
Do not dream your life, but live your dreams.

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COMMENTARY

The salience network is functionally twice as large in depression: The first depression biomarker?

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Keywords: Depression, salience network, biomarker, neuroimaging, functional connectivity, brain plasticity

This commentary examines recent findings demonstrating that individuals with depression exhibit a functionally expanded salience network compared to non-depressed controls. Neuroimaging data reveals this network expansion predates symptom onset and remains stable regardless of symptom severity or treatment interventions. The authors propose this distinctive neural signature as a potential biomarker for depression risk, enabling earlier identification and intervention. They discuss three potential mechanisms underlying this expansion: compensatory network changes, genetic predisposition, and relative expansion secondary to atrophy in other brain regions. The commentary emphasizes the need to conceptualize depression as a disorder of neural connectivity rather than isolated neurotransmitter imbalances, with implications for developing targeted therapeutic approaches.

Depression is a neuropsychiatric condition defined by persistent low mood and the inability to experience pleasure, significantly impacting an individual's overall well-being. Despite depression being one of the most common contributors to the global disease burden and the leading cause of health-related disability, the neurobiological mechanisms underlying this disorder remain poorly understood from the perspective of neural network systems (1, 2). While the roles of isolated brain areas and neurotransmitters in depression have been relatively well explored, there remains a lack of understanding of the functional interactions among these systems and how these interactions evolve (1). Furthermore, the majority of research to date has focused on cross-sectional data (1). As a result, despite the burden on people's lives, the economy, and the medical resources that depression inflicts, its genesis and evolution over time at the system level remain unclear. The absence of this information prevents the understanding of depression and potential therapeutics from progressing (1). This is where the recent Nature paper, Frontostriatal Salience Network Expansion in Individuals with Depression by Lynch et al. makes a significant contribution, shedding light on the functional connectivity of neural networks in depression (1).

Lynch et al. used functional magnetic resonance imaging (fMRI) to measure communication among brain areas by analyzing the synchronous activity levels over multiple sessions over time (1, 3). Their results demonstrated that, compared to those without a history of depression, nearly every individual with a current or a history of depression illustrated a salience network, which, by synchronous activity, was almost twice as large as that of non-depressed controls (3). The salience network consists of the fronto-insular cortex, the dorsal anterior cingulate cortex, the amygdala, and the temporal poles (4). This network has been implicated in reward processing and regulating the switch between the default mode network and the frontoparietal network depending on the salience of stimuli and how the stimuli align with the internal goals of the person (3, 5).

Lynch et al. question whether the topology of the salience network varied with the severity of depression symptoms. Subsequently, they found that quick-acting antidepressant treatment (repetitive transcranial magnetic stimulation [rTMS]), frequency of depressive episodes, and the severity of their symptoms changed the topology of the salience network. Lynch et al. concluded that the increased functional size of the salience network was characteristic of individuals with depression but that it was not indicative of the time course or severity of the disease. This led them to speculate that the expansion of this network predated and stood as a potential trait biomarker for depression as opposed to single-handedly underlying or causing depression. To test this theory, they subsequently analyzed the brains of children (between the ages of 9 and young adulthood) before the onset of depressive symptoms. They discovered that children who ultimately went on to be diagnosed with depression had expanded salience networks when compared with those who were not. Collectively, these findings illustrate that the functional enlargement of the salience network is a characteristic feature of brain network organization among people predisposed to depression. Furthermore, this distinctive feature predates the onset of symptoms of depression, is stable, and is unaffected by fluctuations in depressive symptoms (1).

Lynch et al. propose two reasons for this expansion of the salience network in those with depression. First, they comment that their findings are consistent with multiple studies that indicate brain network topology distribution is a compensatory response based on use and that individuals who go on to develop depression are those who have relatively increased usage of this network (6, 7). Second, they postulate that there could be a genetic predisposition to developing an enlarged salience network in individuals who will go on to develop depression (1). Based on previous research that has consistently found significant atrophy in the brains of individuals with depression, we propose a third explanation (8). Specifically, we propose that the salience network could appear to be relatively functionally expanded as a consequence of atrophy of other brain areas that could also predate depressive symptoms (8, 9). While Lynch et al. commented that the salience network may be enlarged to compensate for the atrophied other areas where connections may not be as strong in their first reason, we propose that perhaps the salience network is functionally enlarged as a secondary consequence of normalization in other areas of the individual's atrophied brain.

It is important to note that there are many similarities between the regions implicated in atrophy in depression and the salience network, including the insular cortex, anterior cingulate cortex, and sections of the prefrontal cortex. However, the hippocampus and striatum are found to be atrophied in individuals with depression and are not found in the salience network (10). Furthermore, while some regions of the prefrontal cortex have been associated with the salience network, atrophy is found to be more widespread throughout the prefrontal cortex in individuals with depression (10). The atrophy of these regions found outside the salience network could account for the appearance of relative functional expansion of the salience network in the paper by Lynch et al.

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Regardless of the foundation of these findings, the topological difference in the salience exists, persists, and predates the onset of depressive symptoms. This suggests that a functionally enlarged salience network could be interpreted as a predictive depression biomarker. The United States National Institute of Health defines a biomarker as a measurable trait indicative of a normal process, a pathogenic one, or in response to intervention (11). Biomarkers in psychiatry remain challenging to characterize due to disorders' overlap and heterogeneous presentation (11). However, despite the heterogeneous presentation of depression, the salience network is observed to be consistently enlarged in those with depression. Those findings suggest that there is potential for identifying individuals at risk of developing the disorder.

Depression remains a poorly predicted and diagnosed disorder despite the significant burden it inflicts. By identifying those at risk of developing the disorder earlier, more strenuous proactive monitoring and preventative measures could be brought to bear, and fewer individuals would fail to receive a diagnosis and, ultimately, treatment. Symptoms of depression have life-lasting physical, professional, and social consequences, particularly with the typical onset of depression falling synchronously with significant life decisions in adolescence (12). By identifying individuals at risk before they experience the full impact of depression, we can intervene earlier, leading to lasting improvements in their quality of life. Finally, early detection has been proven to support remission in those with depressive symptoms and decrease the likelihood of progression to treatment resistance, ultimately lessening the likelihood of relapse, longer depressive episodes, and shorter periods of remission (13, 14).

Additionally, it is important to consider the strong association between adverse life events and later life psychopathology (15). Adverse life events are also associated with functional and morphological changes in brain regions found in the salience network (16). This raises the question as to whether the enlarged salience network and the increased risk of depression associated with it, found by Lynch et al., are simply an effect of these adverse events. However, while previous work has illustrated dysfunction in the salience network in a multitude of cognitive disorders associated with adverse life events, the dysfunction of the salience network presents on a spectrum of hypo and hyperactivity in varying psychiatric disorders (5). Specifically, past work demonstrates hyperactivity in the network in individuals with PTSD, a mix of hyper and hypoactivity in anxiety, and hypoactivity in anorexia nervosa (17–19). Therefore, while dysfunctional connectivity in the salience network presents in a majority of individuals with psychiatric disorders strongly associated with adverse life events, the exact dysfunctions appear to vary across multiple psychiatric presentations.

In addition to identifying individuals at risk for depression earlier, these findings hold the potential to inform the development of depression therapeutics that target the reduction in functional connectivity in the salience network. While Lynch et al. found that a larger salience network was characteristic of individuals with depression but not indicative of the time course or severity of the disease, it remains unclear if we can modulate the network's size with any therapeutics other than rTMS (as rTMS was found to have no impact), and if so, how would this impact the course of disease in individuals. There could be value in investigating the effects of other established and novel treatments for depression, including antidepressants, exercise, diet, electroconvulsive therapy, ketamine, and psychedelics, among others, as emerging studies have found that all the above have been implicated in the central nervous system plasticity (20–22). In particular, one day after psilocybin therapy, a significant reduction in the default mode network (DMN) recruitment was observed, with increased between-network integration between the DMN and salience network (23). Specifically, longitudinal studies tracking how the size of the salience network evolves with different treatment modalities could provide transformative insights into whether external stimuli can modify this network, the impact of these interventions on the network at various stages of life, and if a reduction in the size of the salience network impacts symptoms of depression. Ultimately, these insights could lead to a more substantial understanding of how external factors alter the salience network and if alterations in this network can lead to improved symptoms of depression, thereby paving the way for the development of improved personalized treatments to mitigate the continued impact of depression.

Depression is not a simple disease characterized by independently functioning brain areas or isolated neurotransmitter imbalances. Instead, by record, it is a multifaceted condition with altered brain-wide connectivity that cannot be comprehensively understood through these fragmented lenses. Furthermore, should the identified expansion in the salience network prove to be related to the likelihood of developing other psychiatric disorders, it could be used as a potential biomarker for the development of these disorders as well, improving outcomes for patients with multiple psychiatric conditions. Future advances in the treatment of depression must recognize that depression is a disease characterized by altered connectivity across the brain versus taking a (too) low-level e.g., 'reductionist' approach. Only then will we make truly incremental advances on addressing the burden of depression at the individual and societal levels.

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THOUGHT LEADERS INVITED REVIEW

The descriptive psychopathology of melancholia in Roubinovitch and Toulouse's 1897 monograph "La Mélancolie"

Kenneth S. Kendler[1], and Virginia Justis[1]

Our modern syndrome of major depression developed over the 19th century and assumed its largely current form in Europe during the last decades of that century. A defining monograph in that historical development in German-speaking Europe was published by Krafft-Ebing in 1874. In this article, we provide a detailed commentary (and an English translation) of key sections of a monograph—"La Mélancolie" (The Melancholy) published by Roubinovitch and Toulouse in 1897—that plays a parallel role in the Francophone world. We emphasize six features of this important document. First, is it thoroughness, covering, with often vivid descriptions, the symptoms, signs, subtypes, course of illness, and outcome of melancholia. Second, this work describes the key features of the evolution of the concept of melancholia over the prior century. Third, we also see in this monograph important references to the leading explanatory psychophysiological model for melancholia developed in the middle third of the 19th century—melancholia as psychalgia or "mental pain." Fourth, the authors are committed to attempting to understand, in psychological terms, key features of the melancholic syndrome and in particular the development of delusions. Fifth, they give great emphasis to a symptom/sign pair in their diagnosis and description of melancholia: psychological suffering accompanied with resignation and "psychophysical decrease." Sixth, these authors attend to the lived experienced of their melancholic patients, considering some key themes, such as derealization, now emphasized in phenomenological studies of depression. Seventh, they have an insightful view of the evolution of psychiatric diagnoses that applies to the modern day—that disease identification in psychiatry lags behind that most parts of medicine as our diagnostic categories are still "only provisional symptomatic groupings which will one day be replaced by more exact conceptions of the nature of the relationships which unite the facts."

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The modern syndrome of major depression/melancholia developed over the course of the 19th century and assumed its largely modern form in Europe during the last quarter of the 19th century (1–4). A key 69-page monograph that helped contribute to the solidification of this syndrome in German-speaking Europe was published by Richard von Krafft-Ebing (1840–1902) (5, 6) in 1874.

Here, we examine a lengthier French monograph published 13 years later by Jacques Roubinovitch (1862–1950) and Édouard Toulouse (1865–1947) (hereafter R&T) entitled simply "La Mélancolie" (The Melancholy) (7) (Figure 1). The book, 420 pages long with 8 chapters and 22 detailed case histories, has received little attention in the Anglophonic literature and, in our view, played a role in the Francophone world broadly comparable to that of Krafft-Ebing's work in the German literature. That is, both present detailed summaries of the depressive syndrome that document its evolution into its broadly current form, although from relatively distinct national psychiatric traditions. Given space limitations, our commentary focuses on the descriptive psychopathology sections of this monograph largely contained in chapters 2 through 4 (pp. 24–234). We present, as online Supplementary Material, an English translation of chapters 1 through 4 and the first part of chapter 5 (pp. 1–271). (Chapters 1 and parts of 5 are included in the translation so readers can review, respectively, the authors' history of melancholia and their views of the etiology of melancholia). We sometimes add italics to our quotations from R&T for emphasis. Quotes that are of interest, but less essential to our narrative, are placed in Table 1. We turn now to brief biographies of the authors.

Biographies of Roubinovitch and Toulouse and Their Collaboration

Jacques Roubinovitch (1862–1950) born in Odessa, Ukraine to a French mother and a Ukrainian-Jewish father, was a gifted psychiatrist and researcher who spent his time working on the improvements of the conditions in psychiatric assistance; however, he was also concerned with the relationship between organic syndromes and psychiatric illnesses (8). He received his doctorate in Paris in 1890, one year after becoming a French citizen. In 1891, he completed his thesis: Hystérie mâle dégénérescence. Roubinovitch, prior to receiving his doctorate, interned at the Asiles de la Seine. In 1894, he was named as Head of the clinic of mental illness at the Faculté de Médicine de Paris. Following this position, he became the head doctor at Bicêtre in 1899.

Throughout his career, he published many works with his contemporaries, such as Édouard Toulouse and their work on melancholia, Gilbert Ballet and their work on urine toxicity in the mentally ill, and E. Phulpin and their work on dementia praecox, among many others. Roubinovitch is also responsible for the French adaptation of Atlas und Grundriss der Psychiatrie by Wilhelm Weygandt in 1904.

Also in 1904, Roubinovitch contributed to the overhauling of the 1893 law on the insane in his role in the Legislative Studies Commission. Later in his career, he focused on the issue of childhood delinquency and worked with the Child Rescue Organization and provided childhood psychiatry consultation at the Henri-Rousselle Hospital.

In 1921, Roubinovitch and his colleague, Toulouse, founded the French League of Mental Hygiene to increase awareness about causes surrounding mental health. Today, this organization still exists under the name Ligue Française pour la Santé Mentale (French League for Mental Health).

During the occupation of France in World War II, Roubinvitch was arrested by the Germans and interned at the Rothschild Hospital, where it is said that he provided comfort to the patients. He died in 1950 in Paris.

Édouard Toulouse (1865–1947) born in Marseille, France was a French psychiatrist, journalist, and eugenicist. In his early life, Toulouse worked

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Table 1. Additional quotations

#	Quotation
1	What sometimes adds to this suffering is that patients remember with remarkable clarity their entire previous emotional life, they then remember that previously, even when they were grieving, they were sensitive to what was happening around them. They could have joyful feelings, sympathize with the pain of others, console others, love; in a word, their affectivity was normal. Whereas, once ill, they became deaf to all the calls [41] coming from the outside world; nothing touches them anymore, nothing moves them. And from this comparison between their previous psychological state and their current state, they conclude that *they have become unworthy beings, monsters having lost all human feeling* (7). p. 40–41.
2	Memory, that is to say the faculty of recalling mental images, is generally weakened in melancholic people … Patients seem to be searching for words, probably because the verbal motor images are too faded to allow easy speech… Motor images are also weak… the melancholic … cannot clearly conceive and consequently execute his desires…. It is impossible for him to engage in the slightest work … As a result of the reduction in his psychomotor functions, the patient loses all confidence in his strength. He no longer formulates desires because it is impossible for him to imagine their realization. Often the patient expresses this reduction in his voluntary power by saying: "I would like to, but I cannot. » This weakening of motor images ultimately affects the processes of volition…. No idea is accompanied by energy great enough to determine the individual in one direction rather than the other…. Indecision is therefore a characteristic feature of the mental state of melancholic people… The slowing down of psychological functions can, in certain cases, go as far as complete cessation. It is then a question of melancholia with stupor (7) p. 61–67
3	… delusional ideas of melancholia can sometimes become systematized … Sometimes it is the ideas of ruin that predominate. The patient is convinced that he has lost everything, his money, his position, his situation in the world, and that he will never be able to get them back; he sometimes refuses food on the pretext that he cannot pay for it. Sometimes we observe ideas of humility. The subject declares that he is nothing, that he is miserable, that he does not deserve the care given to him and he does not understand how anyone is interested in him. From there to ideas of guilt, there is only one step; and this step is very often taken. The subject is then a serious criminal. He is the cause of all the evil that happens on earth. If people around him suffer, it is his fault. A patient in a hospital ward … accused herself of contributing to the end of her roommates; it was her breath that carried death around her. Sometimes this delusion of self-accusation takes on a particular intensity. And we hear patients declaring themselves guilty of misdeeds they never committed….Hypochondriac ideas are often associated with melancholic delusions… The patients believe they have an obstructed digestive tract, they complain of not being able to urinate, of having their anus turned upside down, they are very concerned functions of this or that organ, and find in these fears about the physical state of their viscera, a new element of delusion (7). pp. 110, 113
4	The means that melancholic people use to commit suicide are numerous. They have varied according to the historical period, and still today they vary depending on whether the subjects are free to move or closely monitored… Each sex has its means. Women hang themselves more willingly, while men prefer sharp weapons and, for example, cut their throats—a delicate maneuver that frequently fails. For hanging, which is often just a simple strangulation, everything is good. Outside a tree, and on a window latch, a nail, the rungs of a ladder, an exposed lead pipe, everything that projects and can hold a tie is used by melancholic people. The link is often a simple rope, a handkerchief, a garter, a scarf…Submersion is mainly used … by women. Poisoning … with laudanum, chemical matches, are common …morphine, arsenic. Some people have tried to die by becoming deeply intoxicated with rum, absinthe or any other alcoholic beverage. More often alcohol is absorbed as providing the stimulation necessary for suicide to occur…. Others throw themselves from a high place, from a window for example (7) p. 138, p. 140–142
5	A lady Do… remembers that she once had a miscarriage. This memory haunts her. Her dreams are filled with painful visions of children having their throats slit. Her anxiety increases, and one fine day she tells herself that she must have had an abortion, that this miscarriage is a very bad thing. She is therefore a criminal; it must be cut into pieces, etc. (7) p. 177.
6	The melancholic hypochondriac, having reached the period of state, becomes an unbearable tyrant for those around him. He demands the presence of his relatives or guardians day and night. … His doctor is naturally one of his first victims. Every day he tires him out for hours by describing to him in detail everything he has experienced since the day before, the new symptoms he has discovered, the medications he has taken; he speaks to him in great detail about his sputum, his urine, his excrement (7). pp. 191–2

as a journalist and a drama critic. He then moved into the sphere of psychiatry, where he focused on melancholia (9). His interest in medicine came about in the late 19th century when he began to study it in Marseille. Toulouse was of the belief that art played a large role in psychology, and used literature to study the mind.

In 1891, he wrote his doctoral thesis: Étude clinique de la mélancolie sénile chez la femme. Toulouse interned at many psychiatric hospitals around Paris at this time, gaining helpful experience and insight.

It is during this time of his life that he encountered Jacques Roubinovitch, and many other colleagues with whom he collaborated to produce a wide array of research into the mind. During his lifetime, Toulouse published over 20 works. Research and journalism remained important to Toulouse, evidenced by his prolific writing.

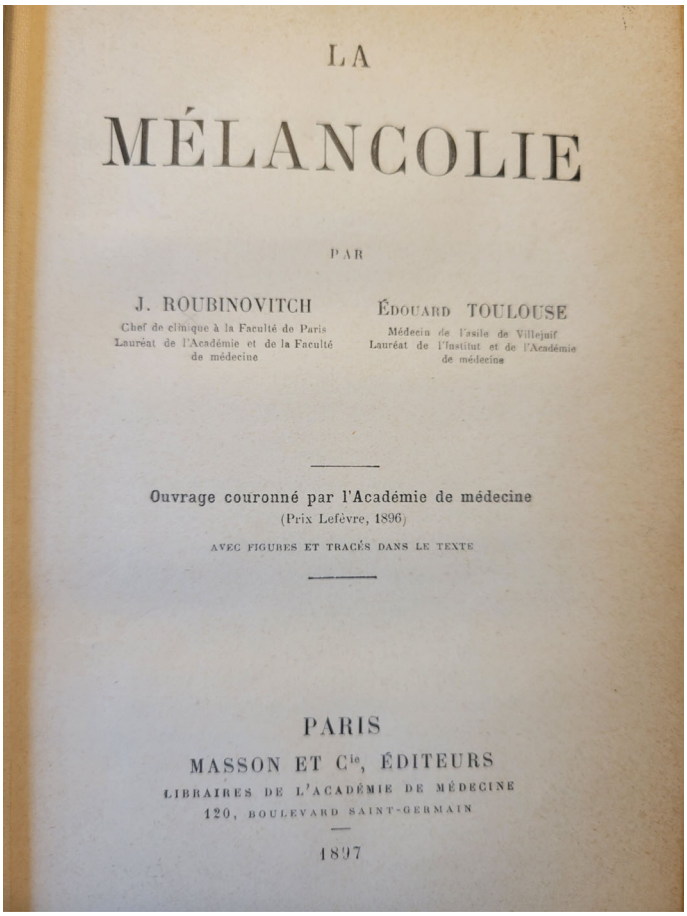
In 1898, he became director of l'Asile Villejuif in a Parisian suburb. While there, he collaborated with other psychiatrists like Henri Piéron and the psychologist Théodule Ribot.

In 1901, Toulouse opened an experimental laboratory to study the convergence of social relations and encounters and psychiatric research. Toulouse was at this point interested in the study of genius, and worked with Émile Zola to understand the link between genius and madness.

Toulouse was also a eugenicist, with a firm belief that motherhood should be reserved only for women in perfect health. He wanted to use his scientific knowledge to make society more reasonable and just (10).

In 1912, Toulouse revisited his love of the arts and established a literary journal, Demain. From 1922 to 1936, Toulouse directed le Centre de prophylaxie mentale du département de Seine. Currently, there is a psychiatric hospital named after him, Le Centre Hospitalier Édouard Toulouse, located in Marseille, France.

Both Toulouse and Roubinovitch worked at Sainte-Anne asylum under the service of Alix Joffroy, whose observations were used in La Mélancolie (7). They chose to write together to share observations to be useful to other practitioners as well as to explore different theories. After the publication of La Mélancolie, Toulouse and Roubinovitch continued to interact. As mentioned above, the two were integral in the forming of the French League for Mental Hygiene in 1920. Roubinovitch's psychiatry consultation career at Henri-Rousselle was also an important location for


LA

MÉLANCOLIE

PAR

J. ROUBINOVITCH
Chef de clinique à la Faculté de Paris
Lauréat de l'Académie et de la Faculté de médecine

ÉDOUARD TOULOUSE
Médecin de l'asile de Villejuif
Lauréat de l'Institut et de l'Académie de médecine

Ouvrage couronné par l'Académie de médecine
(Prix Lefèvre, 1896)
AVEC FIGURES ET TRACÉS DANS LE TEXTE

PARIS
MASSON ET Cie, ÉDITEURS
LIBRAIRES DE L'ACADÉMIE DE MÉDECINE
120, BOULEVARD SAINT-GERMAIN

1897

Figure 1. Roubinovitch and Toulouse's 1897 monograph "La Mélancolie".

Toulouse—it is where he set up the first free outpatient psychiatry service. Starting in 1932, the two also collaborated, as part of the 27 psychologists, psychiatrists, and anthropologists, in the Society of biotypology (10) for the goal of gathering research across many disciplines to have a more complete idea of the "individual." The same year, Toulouse introduced the Society of criminal prophylaxis, and he asked Roubinovitch to contribute his knowledge on delinquent youths.

Background

In their introductory chapter on the history of Melancholia, R&T make a few points that put their further discussion into context. With respect to their approach compared with the very broad definition of melancholy, sometimes noted in earlier in the 19th century French writings, they wrote:

> By such a definition of melancholia its circle is noticeably narrowed; because to justify such a diagnosis *it is no longer enough to simply be dejected and in a state of sadness; In addition, a whole set of symptoms with a special evolution is required* (7). p. 15

In modern terms, they argue that melancholia is a biomedical syndrome quite distinct from isolated mood states of sadness. How similar is their approach to melancholia to contemporary writings in the German and Anglophonic literatures? Their views are quite close to "how melancholia seems to be understood today by the majority of French and foreign alienists (7). p. 15." They continue

> One of us did a particular study on this question (11). We will limit ourselves to citing the German alienists who have carried out extensive research on this subject. From a clinical point of view, *they understand melancholia almost as we do* (7), pp. 16–17

R&T then discuss whether melancholy really qualifies as a "morbid entity"

> ...must we not admit that what the authors call melancholia is a heterogeneous compound of physical and psychological disorders, which no natural link unites, something comparable to the chest inflammation or the cerebral fever of the ancients? (7) p. 24

They review the long debate about the homogeneity versus heterogeneity of melancholy, noting that psychiatry differs from medicine which in their era was making great progress with the identification of many specific diseases related to specific microbial agents:

> We cannot, in mental pathology, *be as rigorous in the categorization of morbid disorders as, thanks to progress in microscopic and bacteriological analysis, it is permitted to be in general medicine* (7) pp. 25–26.

R&T continue

> But, in psychiatry, what can we use to delineate a morbid state? It is not about the microbe, nor about experimental transmission—as in infections; nor is it about the visceral lesion, which is still unknown. *So is it necessary to forbid ourselves from any study of phenomena, because they are more complex than elsewhere? No, certainly; and we are obliged to create morbid categories, as naturally or rather as less artificially as possible.* This, without hiding the fact that these are probably *only provisional symptomatic groupings* which will one day be replaced by more exact conceptions of the nature of the relationships which unite the facts (7). p. 25

Their approach is rather Kraepelinian in tone, echoing his position that psychiatry in this era needed to initially use clinical research methods—studying symptoms, signs, and course—to define syndromes and then hope validation will occur from other sources—like physiological, postmortem, or genetic studies (12).

R&T then discuss the core symptom of depression "what characterizes melancholia is sadness (7) p. 27." They reject the earlier 19th century definition of melancholia which required psychotic symptoms:

> What, then, characterizes it [melancholia] more specifically? It is not delusion, since it can be absent, the subject nonetheless remaining a lypemaniac [a synonym for melancholic introduced by Esquirol]: we then say that it is a question of melancholia without delusion. On the other hand, delusional conceptions of a sad nature are encountered in a host of illnesses without dominating the scene and making one think of lypemania. But if melancholic delusion is not necessary for the diagnosis, even more so are morbid conceptions of negation, of immortality, of hallucinations, all of which may or may not exist in the mental disorders that we are trying to characterize (7) pp. 27–28.

They then present a clear definition of their understanding of the core of the melancholic syndrome:

> There are other characteristics, these constant ones, and which are pathognomonic, especially in their association, of what we call melancholia. *It is the mental pain and the slowing down of mental functions*.... Mental pain, even more than the cessation of the mental faculties, is the attribute of the melancholic. It is the pain which creates this constant sadness even under ... the paroxysms of anxiety. And we can say that *melancholia is above all a pathologically sad emotion* (7). p. 28

They elaborate to help differentiate melancholia from the generic sadness that often accompanies other forms of psychiatric illness, especially in their history:

> This *psychological suffering must still present itself with particular characteristics, and—to put it straight away—with a certain resignation*.... The individual no longer receives from all his organs, from all his tissues, the usual sensations which accompany the state of health... This change in perceptions determines a distressing emotional tone (7) pp. 28–29

R&T here give a clinical pointer to help in the differential diagnosis of melancholia from the nonspecific sadness common in early stages of psychotic disorders: "For far from accusing others, he [the true melancholic] accuses himself to the point of usually seeking an end to his ills in suicide (7) p. 31."

In addition to the sad mood, they reemphasize what they above called "slowing down of mental functions" in melancholia:

> Mental arrest, which starts from simple dulling and ends in complete stupor with or without delusion, is an almost equally constant phenomenon.... We are therefore armed with two criterial signs sufficient to limit the clinical field of melancholia: psychological suffering and psycho-physical decrease. The first especially, psychological suffering with resignation, is absolutely characteristic of the illness (7) pp. 31–32

Chapter III – Symptomatology

In this chapter, R&T examine the melancholic syndrome in greater detail:

> After examining the constant psychological and physical symptoms, we will study the inconstant ones, those which, like hallucinations, various delusional ideas, acts, are contingent, and may or may not be present without altering the diagnosis of melancholia (7) pp. 31–8

Symptomatology – Consistent Symptoms

They provide, at the start of this chapter, a formal definition of melancholia:

> it is a *state of sadness without sufficient reason* with a tendency to *resignation,* a state of which *psychological suffering* is the fundamental symptom. To this sign is added another no less important one: *the slowing down of psychological processes*, which in certain cases can go as far as complete cessation. (7) p. 39

It is worth taking this pithy definition apart. Is melancholia fundamentally what we would now call a mood disorder? This was not obvious for much of the 19th century. R&T are, however, here, making their position clear. However, to preserve the idea that melancholia is a mental disorder, they add an important caveat which has been present in many but not all definitions of melancholia in the 19th century (13). That is, they exclude from their definition cases where the depressed mood arises with "sufficient reason." To anticipate by several decades the position of Karl Jaspers (14, 15), depressive episodes that were psychologically understandable reactions to overt stressors would not meet R&T's definition of melancholia.

R&T provide the reader with further information to distinguish a normative depressive reaction from melancholia:

> The psychological suffering of the melancholic is a chronic painful emotion, which, in serious cases, gradually invades the entire field of consciousness. Is there a difference between this psychological suffering and that which occurs in a normal individual under the influence of a reasonable motive? ... in the normal individual with excessive grief, *the possibility of receiving pleasant perceptions still remains*, and there remains *some hope of emerging from the painful phase* he is going through. The true melancholic has completely lost the faculty of experiencing sensations which can distract from his sorrow; and he is convinced that he will never be able to get rid of his psychological suffering. He no longer sees any favorable solution; there is *a real wall between him and the outside world against which all hope is shattered* (7). pp. 29–40

So, they find that complete anhedonia and the state of hopelessness are important distinguishing features of reactive depressive states and melancholia. Furthermore, the qualitative feeling of the depression differs:

> *The intensity of this suffering makes it unlike any other*. The recovered melancholic people we interviewed always told us that the pain they experienced could not be compared to any physical pain (7) p. 40

For a poignant description of the reactivity in "normative grieving" versus the pervasive anhedonia of melancholia, see Table 1 quote 1. R&T did not consider severity of mood disturbance a necessary requirement for a diagnosis of melancholia. Milder cases of illness could also be considered as disordered:

> Certainly, there are melancholic states in which everything *is limited to mild pain*. What then allows it to be considered pathological is the absence of sufficient reasons and also the patient's belief that he no longer has the same emotional sensitivity as before. Moreover, the intensity of this psychological suffering is not always equal in the same individual. There are oscillations; and, on the same day, the melancholic can feel more distressed in the morning than in the evening ... , *this mental suffering always has the characteristics of being accompanied by a feeling of resignation, of helplessness* (7) pp. 41–3.

Note the description of classical diurnal mood variation frequent in 20th and 21st century descriptions of melancholia.

R&T then turn to providing a psychophysiological explanation of the origins of the mental pain characteristic of melancholia. Here they use the unusual term *coenesthesia* which is defined as "the blend of numerous bodily sensations that produces an implicit awareness of being alive and of being in a particular physical condition:"

> *Let us now try to show how the psychological suffering of the lypemaniac arises and develops and on what it is based.* We have already said that it was necessary to suppose at the origin of a melancholic state ... *The thousand sensations, which continually come from all the organs, are no longer the same. The coenesthetic sense ... is ... altered.* The patient no longer recognizes his usual sensations; *he no longer feels like he is living as before*..... We can in this way explain how simple alterations of coenesthesia can cause somewhat serious discomfort. In addition, sensory sensitivities (vision, hearing, etc.) undergo similar alterations in their functioning. It is then *that patients say that they feel transformed and that they no longer see the outside world in the same way*.... The patient isolates himself, since all external impressions arouse and maintain his suffering. These modifications in internal and external perceptions do not occur with impunity; and the patient is surprised and suffers from this alteration of his sensations. *The melancholic always has his thoughts concentrated on unpleasant mental representations* (7) pp. 43–44

We need to unpack this important paragraph. R&T focus on a proposed psychophysiological theory for melancholia. Fundamental to this theory is the proposed changes that occur in the bodily physical sensations and internal and external perceptions and subsequent representations that are typically associated with a sense of well-being. These are all dramatically changed in melancholia, causing a cascading set of changes that produce physical discomfort, psychological distress, and depression. These developments are also responsible for the sense of derealization that often accompanies the disorder—the ill individual feeling a substantial change in their lived experienced. Their physical and social world has shifted as have the mental representations that populate their inner life. We outline below how these descriptions echo a key earlier theory in 19th century psychiatry of melancholia and a form of psychalgia. (16)

From symptoms, R&T then move to describe the main "physical" features of melancholia:

> What then are the signs of sadness, to which we usually compare melancholia?... What is characteristic is first of all *an action paralyzing the muscles. The movements are difficult and painful, hence a feeling of discouragement*. The *voice is weak, the gestures are slow, the gait is unsteady; the features of the face sag.... The pulse and breathing slow down* .... (7) pp. 52, 54

They then explore the psychological origins of depressive delusions—assuming the individual unconsciously seeks explanations for their psychological and associated somatic mood state in their prior actions.

> Among the consequences of this mental suffering, we must note the feeling of *helplessness* which invades the patient. When psychological pain is at its maximum, sensory perceptions and ideas lose all pleasant or unpleasant meaning for the melancholic, and the individual falls into a true emotional anesthesia.... But before arriving there, *the melancholic questions himself, and, in this perpetual need for explanations which is specific to the human mind, even when sick, he finds, in the path of passive resignation indicated above, reasons to his sufferings*; this is *the origin of the delusional ideas* ... In this the patient *reasons logically*. As he is in a somatic state analogous to that which accompanies remorse, these come naturally to his mind. To justify them, he accuses himself of imaginary misdeeds; he says he is a great culprit, having committed serious mistakes. (7) p. 58

To recapitulate their point here, R&T argue that the melancholia individual, from a somatic and psychological perspective, feel they are in a state of remorse. How could this be, they wonder. Surely, it then follows,

Figure 2. A melancholic patient p. 71 of volume.

I must have done things for which I should be remorseful—I must have been a bad person …

They then turn to examine what they call the "mental decline" associated with melancholia:

> In the melancholic, we observe a *general slowing down of psychological processes*, which is probably related to the *somatic conditions of sadness*. We have seen that sad emotions could be psychologically characterized by difficult associations of ideas; the two phenomena, *sadness and mental slowness*, would therefore be linked. Clinically we know that in all painful emotions there is a certain cerebral torpor: the head seems empty, according to the expression of patients.… What is certain is that *all mental processes are slowed down and weakened in the melancholic: perceptions, memory, ideation, attention, judgment, even imagination, [and] especially will*. (7) p. 60

To see a description of these features in more detail, see quote 2 in Table 1.

R&T then review the signs of melancholia, illustrating the facial expression and posture by a poignant photograph (Figure 2). They write:

> *The physiognomy of melancholic people expresses their psychological suffering and their lack of energy*. The eyebrows are contracted, vertical folds are formed immediately above the root of the nose; *the forehead presents horizontal wrinkles as a result of prolonged contraction of the frontalis muscle; the angles of the mouth are lowered, the mouth itself is tight;* the face, aged, seems longer than normal (7) pp. 72–3

They continue:

> This reduction in motor skills is seen on the patient's sagging features; it also manifests itself in his immobility. The muscles are often trembling, which indicates that the contraction is hesitant .. the voice is furthermore dull, monotonous, indistinct (7) p. 73

Sleep problems are prominent features of the disorder:

> Among the physical symptoms that appear at the very beginning of melancholia, *sleep disorders should be noted. These are persistent insomnia* … often accompanied by sudden awakenings. In other cases, the individual notices that, even after sleeping, he wakes up in the morning as tired as the night before; *sleep then ceases to be restorative*. (7) p. 75

They follow with a 17-page description, complete with figures, of physiological measures of the changes in respiratory and cardiac function as well as body temperature and urine volume and composition in melancholic pts (pp. 78–95). They conclude this section by noting the frequency of amenorrhea and weight loss:

> Menstrual functions are often stopped, especially in the stuporous.… more or less rapid malnutrition is the consequence of all these functional disorders… [and] consequences of this reduction in nutrition is a lesser resistance to infectious diseases and in particular to tuberculosis. (7) p. 96

Symptomatology – Variable Symptoms

R&T turn to examining "…the symptoms of melancholia which do not have the constancy of those we have just reviewed (7) p. 98," beginning with auditory hallucinations. When present, the content is almost always derogatory:

> Almost always the voices say *unpleasant things*. These are crude insults, where the same filthy words are constantly found. These are threats, sinister warnings, which only increase the depression or anxiety of patients. (7) p. 101.

Interestingly, the hallucinations can blend into thought withdrawal and thought echo—among the classic so-called Schneiderian symptoms which were actually commonly described in the 19th century psychiatric literature (17).

> … the patient says that his thoughts are being stolen from him, that he cannot think of anything without a voice immediately repeating in his ear what he is thinking. In other cases, they overhear dialogues between the subject and imaginary people (7) p. 102.

They then describe the typical melancholic delusions, noting the resigned acceptance of these beliefs rather than the active defiance typically seen in cases with primary psychotic disorders:

> Delusion is a frequent element of melancholia, but not constant. There are clinical forms where patients do not manifest any delusional conception. But there are others—very numerous and varied—where melancholic ideas are clearly delusional… The melancholic delusion *is of a distressing nature*; and whatever form, whatever color it takes on, it is *always a sort of nightmare*. Such a patient says he is abandoned by everyone; another believes that all his relatives are dead; he hears utterances of terrible threats against him; this one is convinced that the scaffold will be erected to guillotine him… Far from recriminating, as the persecuted constantly do, and trying to take revenge on the people to whom they attribute the evils with which they are overwhelmed, *they submit, resigned*. (7) pp. 108–9

For a poignant description of the common delusional themes of melancholic patients, see Table 1, quote 3.

In addition to these more typical delusional themes, R&T note "… other delusional ideas which are rarer and which are elements simply associated with distinctly melancholic conceptions. p. 116" These included delusions of damnation, persecution and more rarely grandeur. That later most typically occur in

> …patients who are rather persecuted. When true melancholic people are ambitious, it is always in their own way. They are great culprits, accusing themselves of all the crimes and all the evils of creation; and if they are a power, it is only an evil, infernal power (7). p. 119

They then turn to consider suicidal ideation:

> …the idea of suicide, which, by the acts it pushes one to commit, is of capital importance. The pathogenesis of these suicidal ideas is very varied. *Despair, remorse, and above all the desire to be rid of psychological suffering are the most common apparent psychological causes of suicide*. Sometimes it is hallucinations which maintain or suddenly provoke these morbid ideas. Other

> times it is anxiety, this paroxysmal mental pain, which suddenly gives rise to the idea of suicide, just as it provokes rapture. But in general, thoughts of suicide have a slow progress and onset.... It should be noted that thoughts of suicide generally have the monotony and steadiness of all the conceptions of [Melancholics]. Patients constantly ruminate on them and design more or less complicated execution plans (7). pp. 114–5.

R&T then turn to "...*acts* which are observed more or less frequently during melancholia. p. 127," the first of which is muteness. They write:

> Mutism is encountered in all forms of melancholia; but *it is much more frequent in the form which is accompanied by stupor*. This is where it is most durable; and it is not rare to observe stuporous people who go months without speaking. ... The causes of melancholic muteness are quite numerous. Sometimes *it is excess suffering* which seems to produce it; the subject is then prostrate, in one of those great silent pains, such as one experiences after terrible emotions. Other times, it is the hallucinations that bind the subject's language. (7) pp. 127–8, 132

Other notable acts in these patients include the refusal of food, self-mutilation, and suicide attempts and deaths. About the latter, they write:

> Suicides are very common during melancholia. They are found in all clinical forms; delusional melancholics and anxious people should *especially be monitored* ... Obviously acts of suicide are the expression of thoughts of suicide; and when these manifest themselves, attempts at execution are to be feared. But it happens that *patients, who do not seem at all to be prey to thoughts of suicide, kill themselves in an unexpected way*. The causes of suicide are quite varied. Sometimes—most often—it is *mental suffering*, which, having become unbearable, panics the patient and pushes him to murder himself... In other cases, it is a particular delusion that causes the impulsions to suicide. A melancholic person wants, by killing himself, to escape the dishonor into which his faults and crimes have plunged him; his death will also be an expiation. He cannot survive the loss of his fortune or his parents. Another rushes into death following a hallucination that commands him to do so. (7) pp. 137–8

R&T review common methods of suicide, which for historic interest, we include in Table 1, quote 4.

Chapter IV – Clinical Varieties of Melancholia

R&T begin this chapter by articulating a distinction between what they call *melancholia-psychosis* and *symptomatic melancholia*. To avoid confusion, we will use the more familiar term of *primary melancholia* for their first subtype, which they define as follows:

> Those where we find no visceral lesions, of the brain or another organ, no nutritional disorder capable of explaining more or less well the appearance of psychological disorders. These melancholies occupy, in mental pathology, a place symmetrical to that held, in neurology, by neuroses. Both appear rather functional or–what is more precise—cannot be linked to any specific lesion (7) p. 145.

Symptomatic melancholia, by contrast, includes cases "where an immediate etiology is very apparent. These include, for example, melancholic states occurring during alcoholism, infections, circumscribed brain lesions (7). p. 146." R&T comment only briefly and this subform of melancholia and we will not consider it further here.

But before describing their four key subtypes of primary melancholia—*stuporous, anxious, delusional, and hypochondriacal*—R&T briefly review what they call simple melancholia, which they note is the form of illness "most often observed outside asylums (7) p. 151." Here is there summary of this syndrome, mirroring descriptions given earlier in the book.

> it is characterized by the reduction of biological energy. Sadness is a most striking objective aspect... This triple difficulty of feeling, thinking, and acting, which asserts itself as the affection evolves, passivity, the absence of any spontaneity, of any psychological activity manifests itself more and more. There may, at times, be a total shutdown of all ideation processes. Not only the patient's actions, but his words, all his movements become slower and slower, more and more difficult... self-consciousness is not deeply affected; it is only invaded by conceptions and images of a sad nature (7) pp. 149–50.

They add that "the patient retains the ability to control and associate his ideas. He generally combines them in the direction that his mental pain gives them (7) p. 150 ..." but delusions do not typically emerge. Furthermore, they note that this form simple melancholia can remit or evolve into more severe forms of illness.

Stuporous Melancholia

R&T begin by describing the typical presentation and course of this subtype:

> For three, four months, the individual is moderately depressed; then the slowing down of psychological processes reaches its maximum intensity, and the patient *falls into a sort of torpor which forces him to complete immobility for days and even weeks*. In this period, he looks like a real statue. *The face loses all expression, the look is vague*; sometimes with a half-open mouth lets the saliva flow, mucus comes out of the nose without the patient trying to blow their nose. The extremities are cold, cyanotic, the arms hang along the body like the sleeves of a jacket, clothes are messy; often the patient urinates and lets out his excrement without moving (7) p. 152–3

It is in such cases, they note, that one of key features of melancholia, the slowing of mental and physiological processes, is most pronounced. They also note important changes in cognitive content:

> From a psychological point of view, the feeling of helplessness is pushed to its extreme limit in the stuporous. And as, on the other hand, the emotional and affective disorder is also at its maximum, it is around these two pivots, *complete helplessness and infinite sadness*, that the psychological state of the melancholic evolves with stupor (7). p. 154

Interestingly, they report the recollections of formally stuporous melancholic subjects:

> *They lived in a world apart, like in a dream. External impressions had virtually no influence on them. They only had a very limited number of ideas, and it was especially difficult for them to produce new ones*. These ideas absorbed them, held them like true obsessions (7). p. 158.

R&T question the clinical coherence of Kahlbaum's formulation of catatonia published in 1874 (18, 19) and note some similarities but important differences between that syndrome and their view of stuporous melancholia. Cataleptic states, a key phase of Kahlbaum's syndrome, can occur, albeit rarely, in melancholia, but are also seen, according to R&T, in a wide-range of other psychiatric syndromes.

Anxious Melancholia

Often,

> ... the onset of this variety is manifested by a change in the character of the individual who becomes sad, irritable, and quite abnormally sensitive. Attributing the cause of his bad mood to his own faults ...he examines the details of his previous life, the more he finds evidence of his guilt or unworthiness. *As the affection develops, the patient becomes agitated in the circle of a small number of painful ideas, usually self-accusing* (7). p. 176

Self-derogatory delusions often emerge and become the focus on the mental life.

> It manifests itself through *the incessant repetition of the same complaints, the same accusations.* Every day, for months, the patient approaches you, explaining with great volubility the two or three misdeeds he blames himself for, the punishment he deserves, the punishment he fears (7). p. 177

For a brief case history, see Table 1, quote 5. R&T then describe the clinical picture of these cases:

> ... he is constantly in motion. He roams his room in all directions and, when he is free, he wanders off aimlessly, simply to satisfy this imperative need to change places, to move continually.... In moments of great anxiety, the patient pulls his fingers, tears his hair, scratches his forehead, cheeks, neck, chest, tears his clothes... During these melancholic paroxysms, he is capable of committing the most dangerous acts: ransacking the furniture, setting fires, tearing out his eyes, ears, genitals (7) ... p. 178

R&T note that young, inexperienced alienists who will sometimes consider these cases to be suffering from mania.

Delusional Melancholia

"Here the disorder," write R&T, "is deeper and the very content of the ideas is more or less altered. In a word, … a new element is introduced: the delusional conception (7) p. 187." Returning to their interest in the causes of depressive delusions, they write

> How is it born? Most often, it is the consequence of a greater intensity of psychological disorders … *It represents the patient's attempt to explain everything painful he experiences* … Clinically, when this state reaches the highest stage of its development, … the melancholic tells himself he is ruined and reduced to begging. He believes he is unworthy of living and incapable. He accuses himself, declaring guilt towards God and men. He feels damned, believing everyone despises him and subjects him to countless insults. Added to this is the fear of punishment, hell, torture, and also ideas of negation, immortality, etc. (7). pp. 187–8

They emphasize the role of psychalgia or mental pain:

> …. all impressions from the outside world arrive in the patient's consciousness profoundly altered; this psychological dysesthesia …. gives all impressions a dark, painful color. This is the source of all the ideas relating to the imaginary dangers which threaten the melancholic and to the equally imaginary persecutions of which he is [often] the victim (7). p. 188

Profound anhedonia also plays a role in the delusional formation, as the patient:

> … becomes incapable of manifesting a feeling of friendship, an aesthetic impression, a religious idea. *As he is perfectly aware of this change occurring in him, he comes to the conclusion that he is no longer a human being, that he is a beast, that God has abandoned him, that he is damned*, etc. (7) p. 189.

At one extreme end of this clinical continuum, Cotard's syndrome emerges: "When psychological anesthesia is at its maximum intensity, the patient imagines that everything around him has disappeared and that he himself is dead (7). pp. 189–190." R&T give an extended discussion of Cotard's syndrome on pp. 196–208. They present a striking image of a delusionally depressed patient in Figure 3.

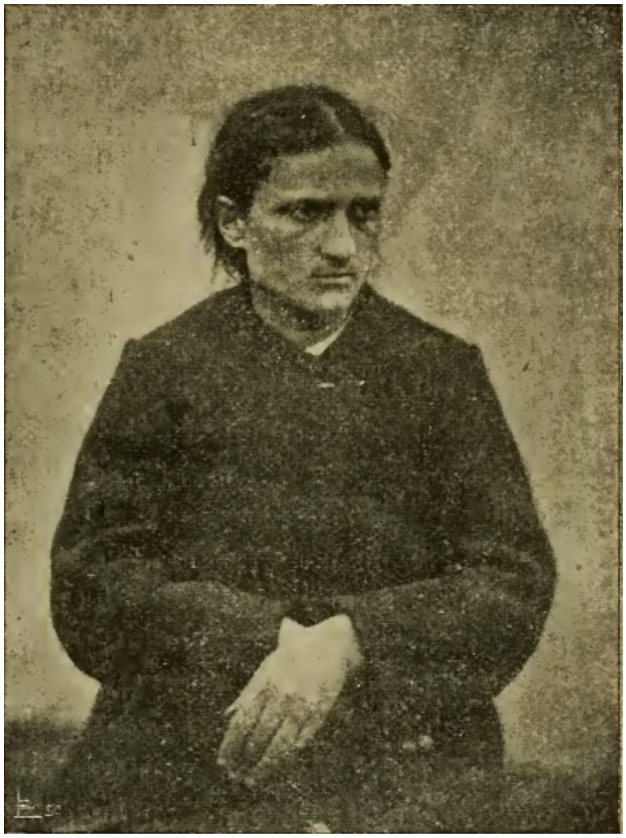


Figure 3. A case of delusional melancholia—p. 189 of the volume.

Hypochondriacal Melancholia

R&T write that

> Certain melancholics, in seeking the cause of their mental pain, *find it not in the impressions they receive from the outside world, but in those which result from disorders of their general or visceral sensitivity*. The gastrointestinal tract and the genitals in particular give them all sorts of painful sensations, which become the starting point for real conceptions of delusional and hypochondriac melancholics. pp. 190–1

The syndrome typically develops in the following sequence:

> The sick are sad, depressed. At first, they cannot give any explanation for their discomfort. But soon, they said they were worried about their health. They feel fatigue, weariness … Sometime later, these still vague sensations become clearer: it's the stomach, it's the gut, it's the chest or even the head that hurts. The most careful medical examination does not allow the discovery of any objective sign in the incriminated organs, and yet the complaints are more and more serious, more and more pressing… under their influence the patient soon abandons his most important affairs, sometimes goes to bed and urgently demands care (7). p. 191

As they outline in Table 1 quote 6, these cases can be very clinically demanding. The course and outcome of such cases is often more severe than most other melancholic subtypes:

> The development of hypochondriac melancholia is often an alternation of bouts of anxiety and periods of depression. The duration is usually long (several months and even several years). The ending is very variable … healing would be observed in a third of cases; another third would pass into a state of chronic hypochondriac melancholia; finally, the last third would slide into dementia (7). p. 193

R&T comment on two particular courses of melancholia, which they term *intermittent* and *circular*. They define the former as follows:

> As a phase of intermittent insanity, this variety is essentially a bout of mental illness which can occur several times in the same patient. In the intervals between bouts the disease seems to have completely disappeared. The bouts appear at regular intervals and present an almost complete resemblance to each other. The patient manifests exactly the same delusional conceptions, the same degree of resignation and abulia (7). p. 212

Circular melancholia, which they said should be viewed in the context of the prior literature on disorders termed "periodic, circular, [and of] double form (7) p. 212"—all of which we would now see as precursors of our current concept of bipolar disorder –they state that they will not address in this monograph.

Finally, we review what R&T write in this chapter on the course and outcome of melancholia. In general:

> the prognosis for depressive melancholia, considered as a whole, is rather favorable. But the prognosis becomes worse when the condition persists beyond a year or eighteen months (7) p. 174.

In mild cases, "the mental disorders can disappear quite quickly, after 3 or 4 months, especially if the subject is subject to a healthy and abundant diet and if you manage to improve your general nutrition. In other cases, and especially in melancholia with stupor, the affection can last a year and beyond (7) p. 172" However, "in other cases, and especially in melancholia with stupor, the affection can last a year and beyond (7). p. 172"

Interestingly, the taking a careful history of their melancholic patients,

> … it is not uncommon to learn that they have had, at different periods of their life, small attacks of melancholia. These attacks lasted a few days, a week or two, then disappeared without apparently leaving a trace (7). p. 172.

These earlier episodes apparently occurred without asylum treatment. In the hospital,

> The progress of depressive melancholia is, in short, uneven. It proceeds in ups and downs, the patient sometimes showing signs of a beginning improvement, sometimes, on the contrary, those of a worsening. It is especially at the beginning and at the end of the illness that we observe these

> oscillations and in particular these aggravations which are very often accompanied by corresponding modifications in the physical state (constipation, insomnia, etc.) (7). p. 173

While generally positive,

> The ending of... melancholia is also very variable. *The most common is healing*. Sometimes also the affection transforms into agitated melancholy or even dementia in people with weak nervous systems, and particularly in adolescents ... Death can finally occur either due to the deep exhaustion into which the melancholic often falls, or also by suicide (7). pp. 173-4.

Discussion

In our view, the monograph on Melancholia by Roubinovitch and Toulouse is an important document in our history of the development of the diagnosis of depression/melancholia that has been surprisingly neglected in the Anglophonic literature. Berrios, typically the most thorough of psychiatric historians, ends his history of mood disorders in the 19th century in France in his major monograph (20) with Falret and Baillarger's key articles in the early 1850s on, respectively, circular insanity and insanity of double form. He is entirely silent on French writings on melancholia in the second half of that critical century. Neither Jackson's classical history of melancholia (21) nor the much more recent and thoughtful volume of Jansson (3) are any better, neither making any reference to the work of R&T. That this neglect might not have always been true is hinted at by a story we uncovered in our extensive search for references to this volume by English-speaking authors. R&Ts volume found its way into the library of William James, the great American psychologist and philosopher. When he was writing lecture V on the "sick soul" in his famous "Varieties of Religious Experience," he consulted R&T noting "I quote now literally from the first case of melancholy on which I lay my hand (22) p. 148."

Of the many major themes touched on by R&T in their monograph, we will here focus on six. The first and most obvious point is the thoroughness demonstrated by the authors in their descriptions. They covered all the major subdivisions within psychopathology often with considerable details: symptoms, signs, subtypes, course of illness, and outcome. Their descriptions of the signs are often vivid ("The eyebrows are contracted, vertical folds are formed immediately above the root of the nose ...in moments of great anxiety, the patient pulls his fingers, tears his hair, scratches his forehead, cheeks, neck, chest, tears his clothes.") The depth of the authors experience and knowledge of the manifestations of melancholia is impressive—more so in reading their full text with case histories than could be conveyed in this summary. The quality of the descriptive psychopathology of this volume is at least as strong as those of other classic descriptions of melancholia/depression in the English (e.g., Lewis (23)) and German traditions (e.g., Kraft-Ebbing (5) and Kraepelin (24)).

Second, we can see in their description, the key developmental features in the evolution of the concept of melancholia from the late 18th century—when it was conceived as a disorder of intellect or judgment, a "partial insanity" often but not always associated with sadness—to its modern form (1, 3, 4). These include, particularly, i) viewing melancholia as primarily a disorder of disturbed mood, ii) the recognition that non-psychotic forms of melancholia exist and are of clinical importance, and iii) the understanding that in the psychotic forms of the illness, the delusions and hallucinations can be understood as resulting from a primary disturbance of mood. We have two additional measures of the degree to which R&T's text aligns with modern concepts of depression. First, clear descriptions of all nine DSM-5 (25) "A criteria" for major depression can easily be found in its pages. Second, in a prior review of 20th century descriptions of depression, one of us (KSK) identified 18 characteristic depressive symptoms and signs from twentieth century psychiatric textbook authors (26). R&T's monograph describes all 18 of them.

Third, we also see in this monograph, important references to the most important explanatory psychophysiological model for melancholia developed in the middle third of the 19th century—melancholia as psychalgia or "mental pain" (16). Briefly, as clinical pathological correlation became a dominant medical paradigm in early 19th century, nervous diseases presented clear exceptions sometimes demonstrating "pain without lesions" or neuralgia, of which Tic Douloureux was the paradigmatic example. This disorder was assumed to result from neuronal hypersensitivity in spinal ganglia so that a normal stimulus (e.g., touch) were misinterpreted as excruciating pain. A parallel framework was conceptualized in the brain to produce psychalgia, thereby explaining how normal social and introspective experiences would, in melancholic patients, be interpreted in a distorted manner which caused mental rather than physical pain and reinforce themes of inadequacy, failure, and worthlessness, and produce a sustained melancholic mood state. We see a number of echoes of this theory in T&R's multiple use of the phrases "mental pain" and "mental suffering." They note that it is the psychalgia "which creates this constant sadness." The patients view of the world is "..no longer the same. all impressions from the outside world arrive in the patient's consciousness profoundly altered; this psychological dysesthesia."

Fourth, R&T attempted at several places in their text, to articulate psychological theories for delusion formation in melancholia: "the melancholic questions himself, and, in this perpetual need for explanations ... he finds, in the path of passive resignation... reasons to his sufferings; this is the origin of the delusional ideas ..." and "it is the consequence of a greater intensity of psychological disorders ... [as] part of the patient an attempt to explain everything painful he experiences. ...The melancholic then tells himself that he is ruined, that he is reduced to begging, that he is unworthy of living..."

Fifth, R&T are somewhat unusual in focusing on a pair of signs as foundational to the melancholic syndrome: psychological suffering accompanied with resignation and "psychophysical decrease."

Sixth, in their writings, these authors attend to the lived experienced of their melancholic patients. They consider themes now commonly emphasized in the phenomenological study of depression—for example, by Ratcliff (27)—including the symptom of derealization—feeling that the world around them has profoundly changed—and the struggles to understand what is happening to them which can, in certain cases, lead to explanatory delusions.

Finally, a series of smaller points are noteworthy. R&T noted that disease identification in psychiatry lagged considerably behind that in certain parts of medicine, especially in infectious disease and agreed that psychiatric diagnostic categories at their time (and ours) were "only provisional symptomatic groupings which will one day be replaced by more exact conceptions of the nature of the relationships which unite the facts." R&T agree with some modern psychopathologists (e.g., refs. 28, 29) that the so-called Schneiderian symptoms, often noted throughout the 19th century (17), were not uncommonly seen in mood disorders and thus are not diagnostically specific to schizophrenia. They noted, importantly, that melancholia—a psychobiological syndrome—is qualitatively different from episodes of sad mood, a diagnostic issue which persists in medical care to this day. They were aware of mild melancholic syndromes—which they termed "simple melancholia"—that did not typically require asylum care. Finally, aware of the problems of the differential diagnosis of reactive depression vs melancholia, they provide sound clinical advice to focus on the assessment of the level of hopelessness and anhedonia.

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Author Contributions

KSK developed the original idea for the paper. VJ, with the assistance of KSK, translated the relevant sections of the book. KSK drafted the main manuscript with the exception of the authors' biographies, which was drafted by VJ. Both reviewed the final context of the manuscript.

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RESEARCH REPORT

Polygenic liability to C-reactive protein defines immunometabolic depression phenotypes and influences antidepressant therapeutic outcomes

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Inflammation has been implicated in the pathophysiology of major depressive disorder (MDD), with elevated serum C-reactive protein (CRP) and CRP polygenic scores (PGSs) previously associated with atypical symptoms and treatment outcomes. However, few studies have examined genetic CRP liability in relation to both depressive symptom profiles and pharmacological response within the same patient cohort. We investigated 1059 Caucasian patients with MDD from the European Group for the Study of Resistant Depression (GSRD) who received ≥ 4 weeks of antidepressant treatment. Depression severity was measured using Montgomery–Åsberg Depression Rating Scale (MADRS), with patients categorized as responders, nonresponders, or treatment-resistant cases. CRP-PGS were computed from individual-level genotypes using L1-penalized regression weights (snpnet) based on UK Biobank Genome-wide association studies (GWAS) training data (n = 223,327), and scores were standardized. Associations were tested through univariable and multivariable models controlling for population stratification and established prognostic variables. Higher CRP-PGS correlated with greater body mass index, lower employment status, and less weight and appetite loss following treatment. Notably, CRP-PGS demonstrated significant differences between treatment outcome groups ($F = 3.52$, $p = 0.03$), with highest values observed in treatment-resistant patients yet also elevated among responders compared to nonresponders, indicating a nonlinear relationship. When controlling for age, episode frequency, suicidal ideation, anxiety comorbidity, employment status, functional disability scores, antipsychotic comedication, illness duration, and previous antidepressant trials, CRP-PGS retained an independent and stronger association with treatment outcome ($F = 7.69$, $p < 0.001$), with CRP-PGS accounting for an additional 1.9% of outcome variance. CRP-related genetic liability may delineate an immunometabolic subtype of MDD characterized by metabolic dysregulation, which may modestly influence therapeutic efficacy. CRP-PGS captures independent prognostic information beyond conventional staging approaches and may facilitate inflammation-guided treatment selection.

Keywords: Major depression, inflammation, C-reactive protein (CRP), treatment-resistant depression (TRD), polygenic risk scores, immunometabolic depression.

Introduction

Major depressive disorder (MDD) is characterized by a variable clinical presentation, illness course, and response to treatment (1–5). A substantial proportion of patients fail to achieve adequate remission with first-line therapies (6, 7). This heterogeneity is linked, at least in part, to biological markers that could predict clinical variability and guide personalized treatment (8).

Genome-wide association studies (GWAS) implicated hundreds of common variants in disease susceptibility (9) but other biological factors modulate depression as well. Inflammatory aspects are in fact well known in depression (10), circulating C-reactive protein (CRP) levels are elevated in roughly one-quarter of depressed patients and track with greater overall symptom burden and cardiometabolic features (11). These observations suggest that pathways regulating CRP could help explain differential patterns of depressive psychopathology and suggest possible personalized therapeutic strategies. Twin and Single Nucleotide Polymorphism (SNP)-based heritability estimates (∼35–40%) indicate a substantial genetic contribution to basal CRP concentrations. The largest trans-ancestry GWAS to date (N ≈ 575 k) mapped 266 independent loci and provides highly powered summary statistics for building polygenic scores (PGS) that capture lifelong liability to higher CRP (12). Such CRP PGSs offer a stable instrument for interrogating inflammation–depression links without the confounding inherent in peripheral protein assays.

Emerging PGS work supports a symptom-specific signal. In three independent cohorts (UK Biobank, MARS, STAR*D), a higher CRP-PGS was associated with neurovegetative symptoms, especially appetite change, fatigue and (to a lesser extent) anhedonia, using network analytic methods (13). More recently, a population-scale Lifelines study showed that a CRP genetic risk score predicted higher negative affect and increased risk of anxiety disorders, extending inflammatory genetic influences beyond somatic symptoms (14). Together, these findings

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Table 1. Correlation of main clinical and sociodemographic variables with CRP-PGS

Variable	Mean ± SD (N)	CRP-PGS[a] correlation (r)	*p*-value	q-value
Age (years)	51.81 ± 13.78 (N = 1057)	0.03	0.354	0.547
MADRS[b] total (retrospective)	34.38 ± 7.53 (N = 1059)	0	0.918	0.918
MADRS total (current)	24.72 ± 11.36 (N = 1059)	0	0.916	0.918
Education	2.78 ± 0.95 (N = 1051)	− 0.04	0.151	0.321
Working status (low to high)	**2.24 ± 1.31 (N = 1054)**	**− 0.06**	**0.047**	**0.160**
BMI[c] (kg/m^2)	**25.69 ± 5.42 (N = 1057)**	**0.07**	**0.016**	**0.160**
SDS[d] Social	6.42 ± 2.66 (N = 1050)	− 0.01	0.78	0.918
Loss of weight (HAMD[e] current)	**0.38 ± 0.65 (N = 1059)**	**− 0.07**	**0.02**	**0.160**
Reduced appetite (MADRS current)	**1.39 ± 1.53 (N = 1059)**	**− 0.06**	**0.044**	**0.160**
Suicidal thoughts (MADRS current)	1.27 ± 1.43 (N = 1059)	0.05	0.084	0.238
Episode duration (days)	215.81 ± 189.43 (N = 918)	0.05	0.099	0.240
Number of depressive episodes	3.59 ± 2.59 (N = 824)	− 0.02	0.538	0.736
Age at onset (years)	**36.93 ± 15.07 (N = 1005)**	**0.06**	**0.046**	**0.160**
Duration of disease (years)	14.97 ± 12.94 (N = 996)	− 0.04	0.253	0.430
Number of hospitalizations	5.27 ± 17.06 (N = 1001)	0.04	0.187	0.353
Suicidal risk	0.89 ± 1.09 (N = 1058)	0.01	0.816	0.918
Side effects total	1.03 ± 0.29 (N = 1058)	− 0.02	0.563	0.736

Bold indicates associations significant at $p < 0.05$. *p*-values are uncorrected given the confirmatory nature of the analysis. Benjamini–Hochberg false discovery rate (FDR) q-values are reported. None survive $q < 0.05$, but the pattern of nominal associations (BMI, weight/appetite, age at onset, and working status) remains consistent with the immunometabolic profile.
[a]CRP-PGS: C-reactive protein polygenic score.
[b]MADRS: Montgomery–Åsberg Depression Rating Scale.
[c]BMI: body mass index.
[d]SDS: Sheehan Disability Scale.
[e]HAMD: Hamilton Depression Rating Scale.

suggest that inflammation-related genetic load may shape a specific immunometabolic depressive profile.

Inflammatory markers have also been linked to pharmacological outcomes. Baseline serum CRP levels differentially predicted response to the selective serotonin reuptake inhibitor (SSRI) escitalopram versus the norepinephrine reuptake Inhibitor (NRI) nortriptyline in the GENDEP trial, with higher CRP favoring noradrenergic therapy (15). Extending this to inherited risk, a higher CRP-PGS modestly interacted with the same two drugs in GENDEP, producing an opposite directional pattern compared with serum CRP and underscoring the importance of disentangling state versus trait inflammation (16). A systematic review of therapy-genetic studies further highlights CRP-PGS as one of the few nonpsychiatric scores repeatedly associated with antidepressant efficacy, although effect sizes remain small and replication limited (17).

Despite these advances, no study has jointly examined how CRP-PGS influences both depressive symptom architecture and treatment response within the same analytic framework. Addressing this gap could clarify whether genetic predisposition to higher CRP delineates a clinically actionable biotype that is prognostic of antidepressant treatment outcome and characterized by a specific constellation of symptoms. Here, we therefore (i) test associations between CRP-PGS and fine-grained depressive symptom dimensions, and (ii) evaluate whether CRP-PGS moderates acute antidepressant efficacy in a large, deeply phenotyped cohort (2). Elucidating these links may inform inflammation-stratified precision approaches in MDD and accelerate development of targeted immunomodulatory interventions.

Results

A total of 1059 Group for the Study of Resistant Depression (GSRD) patients with MDD had complete data and were included in the analysis. Table 1 reports the correlations of CRP-PGS with main clinical and sociodemographic variables.

Higher CRP-PGS was significantly associated with increased body mass index (BMI; $p = 0.016$), lower employment status ($p = 0.047$), earlier age at onset ($p = 0.046$), less weight and appetite reduction after treatment ($p = 0.02$ and $p = 0.044$, respectively) (Table 1). No associations were observed with overall depressive severity [current or retrospective Montgomery-Åsberg Depression Rating Scale (MADRS) total], episode duration, or total side effect burden. Full correlation results are provided in Supplementary Table S1. Across individual symptom domains, CRP-PGS did not correlate with core affective symptoms (e.g., sadness, pessimism, and anhedonia), anxiety symptoms, or cognitive impairment. There was a trend toward higher CRP-PGS in patients with greater suicidal thoughts ($p = 0.084$), though this did not reach significance. Functional impairment and clinician-rated side effect domains showed no evidence of association with CRP-PGS.

CRP-PGS was associated with treatment outcome ($F = 3.52$, $p = 0.03$) with highest mean scores in treatment-resistant patients, followed by responders, and lowest in nonresponders (Figure 1; Supplementary

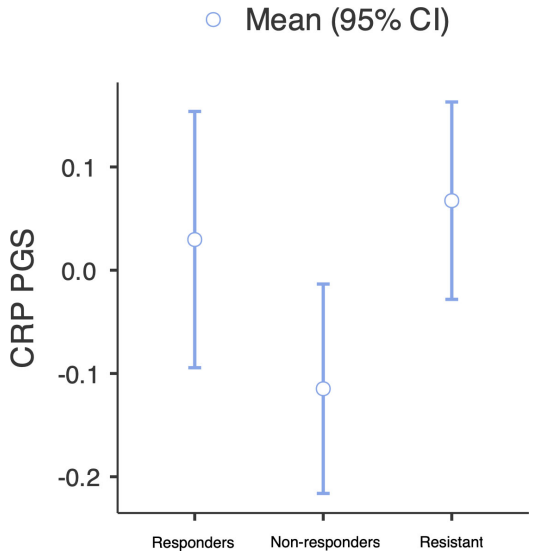

Figure 1. CRP-PGS and treatment outcome. Highest mean scores are observed in treatment-resistant patients, followed by responders, and lowest in non-responders.

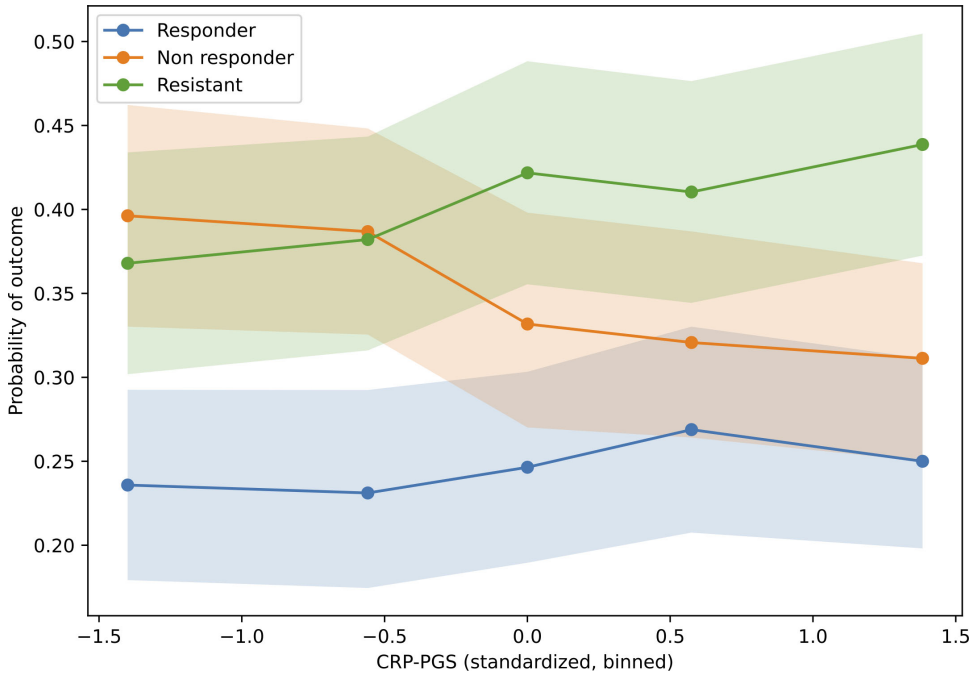

Figure 2. Observed outcome probabilities by CRP-PGS quintile with 95% bootstrap CI.

Tables S2 and S3), indicating a nonlinear pattern across treatment outcome categories. Given the nonlinear pattern, we tested a quadratic regression model (generalized linear model [GLM] with identity link), the quadratic term was statistically significant (β=0.16, $p = 0.013$), confirming a U-shaped relationship, with CRP-PGS levels lowest among nonresponders and higher among both responders and treatment-resistant patients. Residual diagnostics indicated no relevant violations of linear regression assumptions. When CRP-PGS was stratified into quintiles, the probability of being a nonresponder was highest in the lowest CRP-PGS quintile and declined thereafter, while both responder and treatment-resistant depression (TRD) probabilities showed a progressive increase at higher quintiles (Figure 2). Bootstrap 95% confidence intervals confirmed the robustness of these patterns. In the multivariable model, adding as covariates the factors previously associated with treatment resistance [age, number of depressive episodes, suicidal risk, anxiety disorders comorbidity, working status, Sheehan Disability Scale (SDS) social score, antipsychotic augmentation, duration of disease, and number of previous antidepressants], CRP-PGS remained independently associated with treatment outcome ($F = 7.69$, $p < 0.001$, PGS-pseudo-$R^2 = 1.9\%$).

Discussion

Our findings support the concept of an immunometabolic subtype of MDD that is partly modulated by common genetic variation influencing CRP. First, the CRP-PGS was positively associated with BMI and socioeconomic adversity and, in line with prior network-based work (13), selectively mapped onto weight-/appetite-related items rather than core mood or cognitive symptoms. Kappelmann *et al*. showed that a virtually identical CRP-PGS predicted increased appetite, fatigue, and anhedonia across three independent cohorts (UK Biobank, MARS, and STAR*D) (13), while the recent Lifelines mega-analysis extended genetic CRP effects to negative affect and anxiety disorders (14). The present replication in a pharmacologically treated sample strengthens the external validity of this symptom signature and supports the view that trait inflammation taps into energy-balance possibly related to reward-processing circuits that cut across traditional diagnostic boundaries. Polygenic scores, however, remain population-level probabilistic tools rather than deterministic tests for individuals, and should be interpreted as risk modifiers whose predictive utility always depends on the clinical context (18).

We also observed a small but significant association between higher CRP-PGS and antidepressant outcome: scores were highest in treatment-resistant patients yet, somewhat paradoxically, also among remitters relative to intermediate nonresponders. A V- or U-shaped pattern has been described before for state CRP, where both very low and very high serum concentrations predicted better outcomes than mid-range values in GENDEP (15). Our data suggest that a similar nonlinear relationship may exist at the level of inherited risk. One possibility is that very high CRP liability "pushes" patients toward more atypical, energy-rich symptom profiles that may respond better to dopaminergic or noradrenergic mechanisms, whereas modest CRP-PGS elevation may undermine serotonergic signaling and promote resistance. Consistent with this idea, Zwicker *et al*. found an interaction between CRP-PGS and drug class in GENDEP—higher scores favored escitalopram over nortriptyline despite the opposite effect for serum CRP (16). Importantly, the variance explained by CRP-PGS in our multivariable model was 1.9%, in line with earlier estimates (0.5–2%) from GENDEP and CAN-BIND (17). Although modest, this effect was independent of established clinical predictors embedded in the GSRD predictors algorithm (2), indicating that genetic inflammation captures information not already coded by chronicity, severity or comorbidity. However, this hypothesis should be tested in future studies.

The CRP-PGS applied in this study was derived from a single-cohort analysis of the UK Biobank using penalized regression (19), rather than from the larger trans-ancestry meta-GWAS of CRP levels (12). Nevertheless, the two GWASs are highly collinear and converge on hepatic endoplasmic reticulum stress, IL-6/JAK–STAT and lipid-metabolism pathways, lending plausibility to a mechanistic link between circulating CRP levels and systemic metabolic regulation. The genetic architecture of CRP is enriched for loci also implicated in cardiometabolic traits, consistent with epidemiological evidence that low-grade inflammation tracks both depressive symptoms and cardiovascular risk (11), suggesting pleiotropic effects that could underpin the excess cardiometabolic morbidity seen in TRD (20). This interpretation is further supported by recent work demonstrating local genetic correlations between insulin resistance-related conditions and neuropsychiatric disorders at immune-metabolic loci (21).

At the therapeutic level, accumulating trial data indicate that patients with high inflammatory burden may benefit from immune-targeted augmentation, for example, the infliximab proof-of-concept study where baseline hs-CRP $>$ 5 mg/L predicted a ~4-point MADRS advantage over

placebo (22), or similar more recent studies (23). On the other hand, a consistent literature showed that higher CRP predicted better than placebo and low CRP predicted worse than placebo, antidepressant effects with add-on anti-inflammatory substances (24): given that most antidepressants share anti-inflammatory effects (10), which are well evident also in severe, nonpsychiatric inflammatory conditions (25), it is possible that nonlinear dynamics in the relationship between CRP and antidepressant response might arise from the individual sensitivity to these mechanisms, and the possible anti-inflammatory effects of the administered drugs. In indirect agreement with this hypothesis, the observation that: (i) PGS for CRP and CRP plasma levels can have opposite effects on antidepressant response (16); (ii) PGS000675 and many other PGS for CRP share a protective effect against the development of postpartum depression (PPD) in patients with MDD (26), despite PPD being associated with immune-inflammatory mechanisms (27) and higher circulating CRP levels (28); suggest that many factors associated with this biomarker and/or its PGS, might have an effect on the antidepressant phenotype. Interestingly, while some studies described a reduction of CRP before/after antidepressant treatment, although unrelated with its antidepressant effect in meta-regression analyses (29), other recent studies measuring CRP with high-sensitivity methods described an increase in high-sensitivity C-reactive protein (hsCRP) proportional to the antidepressant effects of both, escitalopram (30), paroxetine (31), and the immunomodulatory interleukin 2 (23). These latter observations again suggest individual effects and a nonlinear association of CRP with depressive psychopathology. Assuming linearity for the CRP association with depression may be even less appropriate when considering treatment nonresponse and treatment resistance, given that failing one, or two or more treatments, predicts very different future outcomes and clinical phenotypes. While a germline CRP-PGS cannot substitute for real-time protein assays in such trials, it could help prescreen individuals more likely to have persistently elevated inflammation even in clinical remission, thereby reducing misclassification when serial blood sampling is impractical. Specifying inflammation as a subtype of MDD in future diagnostic systems such as DSM-6 has recently been proposed (32), and tools such as CRP-PGS could play a supporting role in stratified care models. Accordingly, future prognostic work could integrate CRP-PGS with serum-CRP measurements so that both lifelong and current inflammatory burden are modelled together, a strategy that has already improved risk discrimination when genetic scores are combined with circulating biomarkers in cardiometabolic disease (33).

The present study comes with some strengths and limitations. Key strengths include (i) the use of a large, well-phenotyped, multicenter cohort (GSRD), (ii) the use of a validated, penalized-regression PGS with no discovery–target sample overlap, and (iii) comprehensive adjustment for known clinical moderators of TRD. Limitations include the cross-sectional design that limits causal inference, the naturalistic treatment that introduces heterogeneity in drug choice, dose and adherence, though this mirrors real-world care. The sample composition is exclusively of European ancestry, limiting generalizability of our findings across ancestries and warranting dedicated replication. Multiple testing was not formally corrected, any multiple testing correction would reduce observed findings to nonsignificant and for the association between CRP-PGS and substance abuse only 5 patients contributed to the significance; replication in an independent prospective cohort is essential.

Taken together, our results support a multilevel inflammation framework in which CRP genetics shape a distinct symptom cluster and partly predict pharmacological outcome. Integrating CRP-PGS with circulating biomarkers, other immune-related PGSs (e.g., for IL-6) and environmental exposures (smoking and adiposity) may boost predictive utility beyond the 2% ceiling reached by single scores. Future work should test for gene $\times$ serum CRP and gene $\times$ drug-class interactions in randomized designs, explore multi-omic signatures (methylation, proteomics, and metabolomics) of high CRP-PGS carriers, evaluate whether combining CRP-PGS with cardiometabolic PGSs improves risk stratification for the cardiometabolic sequelae of MDD, a major source of excess mortality.

In conclusion, a higher genetic propensity for elevated CRP delineates a small but clinically relevant component of depression heterogeneity that may modulate symptom expression and treatment response. Leveraging this information, if confirmed, in precision-psychiatry pipelines could help move beyond "one-size-fits-all" antidepressant prescribing toward inflammation-stratified care (34–36).

Methods

Sample and phenotypic characterization

Patients included in the present research were collected as part of the cross-sectional, naturalistic, multicenter European GSRD study. As detailed elsewhere (2, 37), adults with current MDD were diagnosed according to DSM IV-TR criteria; participants were naturalistically treated with at least one antidepressant drug at a sufficient dose for at least 4 weeks. Demographic and clinical data were collected as previously reported (37, 38). The MADRS (39) was administered at inclusion and to assess retrospectively symptoms at the beginning of the current episode (considering patients' interview and medical records). Patients were classified as responders if a reduction in total MADRS score $\geq$ 50% from baseline was obtained after $\geq$ 4 weeks of treatment; otherwise, they were considered as nonresponders. In case of nonresponse after two or more trials, patients were defined as TRD. Additional assessments included the SDS (40), Mini-International Neuropsychiatric Interview (MINI) (41), Hamilton Depression Rating Scale (HAMD) (42), and the Committee of Clinical Investigations side effect scale (43). All procedures of this study comply with the Helsinki Declaration and were approved by the local ethics committees of each research center involved in the study (coordinating center approval number: B406201213479). Written informed consent was provided by all patients included in this study.

Genotyping and quality control of the target dataset Genome-wide genotyping in GSRD was performed using the Illumina Infinium PsychArray 24 BeadChip (Illumina, Inc., San Diego) as previously reported (44). Briefly, SNPs and subjects were removed with a missing genotype rate $\geq$ 5%, genotyping rate $<$ 97%, sex discrepancies, abnormal heterozygosity, population outliers or high relatedness (identity by descent $>$ 0.1875) (45, 46). Minimac3 and reference data from the Haplotype Reference Consortium (HRC) r1.1 2016 were used for imputation. Variants with minor allele frequency $<$ 0.01, poor imputation quality ($r^2 < 0.30$), and genotype probability $<$ 0.90 were eliminated (47).

Statistical analyses CRP-PGS were computed using publicly available penalized regression weights derived from UK Biobank, as described by Sinnott-Armstrong *et al.* (19). Specifically, the PGS coefficients were obtained from the BASIL algorithm implemented in the snpnet R package, which applies L1-penalized multivariate regression (lasso) on high-dimensional genotype data. A UK Biobank subcohort including Europeans individuals only (N = 319,074; 70% training, 10% validation, 20% test split) was used to train and validate the prediction models for 35 biomarkers, including log-transformed CRP levels (19). The CRP-PGS used in this study is based on the optimal lasso model trained on 223,327 individuals and validated in an independent test set of 63,818 individuals. The model achieved an R^2 of 0.1215 for log-transformed CRP in the test set, indicating a robust predictive capacity for genetic liability to elevated CRP levels. Coefficients (BETA) for approximately 1.08 million variants were released through PGS Catalog entry PGS000675, and CRP-PGS were calculated in the target GSRD sample using the PLINK2 –score function (48). CRP-PGS were standardized and then were used as independent variables in univariable (correlations, *t* test, and analysis of variance) and multivariable analyses (general linear models and quadratic term) including previously reported predictors (2), adjusting for two population principal components (49). All analyses were performed using Python version 3 for MacOS (pandas, numpy, scipy.stats, statsmodels, and matplotlib) (50) and PLINK2 (48). The statistical significance level was set at $p = 0.05$, uncorrected because of the confirmative nature of the analysis given the previously reported studies on CRP-PGS and depression (51).

Data availability

The data are not publicly available due to privacy and ethical restrictions.

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Author contributions

AS oversaw the entire work, conducted and designed all analyses and wrote the manuscript. DS, SK, LB, JZ, SM, PF, DR, RF, GF, CF, RZ, FB, BB, and JM collected data, oversaw stages of the project and revised the manuscript. The manuscript has been read and approved by all authors. All authors take full responsibility for all data, figures, and text and approve the content and submission of the study. No related work is under consideration elsewhere. All authors state that all unprocessed data are available, and all figures provide accurate presentations of the original data. Corresponding authors: Professor AS for any aspect of the work and data analyses. The corresponding author takes full responsibility for the submission process.

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DR served as consultant for Janssen, received honoraria from Boehringer-Ingelheim, Gerot Lannacher, Janssen, and Pharmagenetix, received research/travel support from Angelini, Boehringer-Ingelheim, Janssen, and Schwabe, and served on advisory boards of AC Immune, Boehringer-Ingelheim, Roche and Rovi. DS has received grant/research support from GlaxoSmithKline and Lundbeck; and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. JM is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. JZ has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultant or on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GlaxoSmithKline, Jazz, and Solvay. AS has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier and Taliaz. SK has received grant/research support from Lundbeck; he has served as a consultant or on advisory boards for Angelini, Biogen, Esai, Janssen, IQVIA, Lundbeck, Mylan, Recordati, Sage and Schwabe; and he has served on speakers bureaus for Aspen Farmaceutica S.A., Angelini, Biogen, Janssen, Lundbeck, Neuraxpharma, Recordati, Sage, Sanofi, Schwabe, Servier and Sun Pharma. BTB received honoraria for serving as a consultant or on advisory boards unrelated to the present work for Angelini, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Meyers Squibb, Janssen, LivaNova, Lundbeck, Medscape, Neurotorium, Novartis, Otsuka, Pfizer, Recordati, Roche, Rovi, Sanofi, Servier, Teva. The other authors declare no potential conflicts of interest. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The manuscript has been read and approved by all authors.

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Shared genetic etiology between childhood cognitive function and longevity

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Cognitive function and longevity are phenotypically and genetically correlated. Whereas molecular genetic data have been used to show that adult cognitive function is genetically correlated with longevity, no such analysis has examined the association between childhood cognitive function and longevity. Using genome-wide association study data on childhood cognitive function (n = 12,441) and on parental longevity (n = 389,166) we found a positive genetic correlation of $r_g = 0.35$ (SE = 0.14, $P = 0.01$) between childhood cognitive function and parental longevity. These results add to the weight of evidence that the phenotypic link between childhood cognitive function and longevity is partly accounted for by shared genetic etiology.

The goal of the research field of cognitive epidemiology (1, 2) is to describe and explain phenotypic associations between cognitive function tested in youth (which largely avoids reverse causation) and later-life health and death. Analyses of long-term follow-up data from large cohorts sourced from the UK, Denmark, Israel, and Sweden show that higher scores on cognitive function tests in youth (childhood, adolescence, or young adulthood) are associated with lower risk of mortality from all causes by mid to late adulthood (2). A systematic review of 16 separate studies, drawing data from over 1 million participants (22,453 deaths) found that, on average, for a 1 standard deviation higher cognitive function test score in youth, there was a 24% (95% CI = 23–25) lower risk of death during a follow-up period of between 17 and 69 years (3).

What causes this association? The cognition-longevity relationship was not confounded by childhood socioeconomic position, was present across a range of cognitive ability, and was present in both men and women (3). There was some attenuation by education and the person's own adult occupational social class.

Might part of the cognition-longevity association be caused by genetic differences? Large genome-wide association studies (GWASs) have been conducted to examine the molecular genetic etiology of people's differences in cognitive function test scores (4, 5). There are also GWASs on longevity (6). These GWAS data enable a comparison between traits; that is, one may compare the loci that attain genome-wide statistical significance in cognition with those that are genome-wide significant in longevity. Furthermore, a genetic correlation between these two traits' GWASs can be derived to describe their average shared genetic effect. One estimate of the genetic link between cognitive function and longevity (obtained by reversing all-cause mortality) is $r_g = 0.37$, SE = 0.06, $P = 0.009$ (4).

However, unlike phenotypic analyses, in which childhood cognitive function is used as a predictor of longevity up to old age, genetic correlations between these variables have been derived using cognitive function assessed in adulthood and older age. This leaves unanswered the question of whether reverse causation/confounding (i.e., that poor health in adulthood and later life influences both cognitive function and longevity) drives some of the genetic association between cognitive function and longevity. The genetic correlation between cognitive function in childhood and cognitive function in adulthood/older age is high but imperfect ($r_g = 0.71$, SE = 0.10) (7). Moreover, the genetic relationship between cognitive function and some health outcomes is dependent on the age at which cognitive function was measured (7).

To date, we are not aware of any genetic correlation having been reported between cognitive function tested in childhood and longevity. In order to address this lacuna in cognitive epidemiology, we use data from two GWASs to estimate the genetic correlation between cognitive function assessed in childhood (8) and longevity (combined mothers' and fathers' attained age) (6).

Applying linkage disequilibrium score regression (for further details see supporting online material) to these GWASs' data, we find that the single nucleotide polymorphism (SNP)-based heritability of childhood cognitive function was 27.3% (SE = 4.7) and the heritability of parental longevity was 28.9% (SE = 0.7). The linkage disequilibrium score regression (LDSC) intercepts for both childhood cognitive function and longevity were close to 1 indicating little inflation due to population stratification.

The principal result from the present analysis is that the genetic correlation between childhood cognitive function and combined-parental attained years was $r_g = 0.35$ (SE = 0.14, $P = 0.01$). This indicates that some of the genetic variants associated with higher childhood cognitive function are also associated with one's parents' living longer.

The current results contribute toward filling a gap in our understanding of cognitive epidemiology and show that, in the absence of reverse causality/confounding, pleiotropy might provide a partial explanation for the phenotypic link between cognitive function and longevity (2).

A limitation of this work is that the presence of a genetic correlation between childhood cognitive function and longevity is consistent with a number of models of pleiotropy, each describe a different genetic relationship between traits that cannot be distinguished from each other with the methods used here. We discuss two forms of pleiotropy below and outline what this would mean for the relationship between cognitive function and longevity.

First, genetic correlations can arise due to horizontal pleiotropy. Horizontal pleiotropy describes instances in which a genetic variant (or group of variants) has two independent effects on the two phenotypes that are genetically correlated. Should horizontal pleiotropy be one of the drivers of this genetic link between cognitive function and longevity, then it would be evidence for the "system integrity" hypothesis, i.e., that more intelligent people tend to live longer and in better health due, in part, to genetic effects producing a body and brain more capable of withstanding environmental insults (9).

Second, the presence of a genetic correlation can sometimes be explained by vertical pleiotropy. Vertical pleiotropy describes instances where two phenotypes are genetically correlated as a consequence of one phenotype's being causally related to the second. In this type of pleiotropy, the genetic correlation between childhood cognitive function and longevity may have arisen, in part, due to childhood cognitive function's providing entry into environments more likely to be conducive to good health. For example, cognitive function has been found to be causally related to education (10) and

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a higher level of education is associated with a higher level of socioeconomic position and less material privation and a greater tendency toward healthier behaviors and higher health literacy.

Furthermore, the genetic correlation derived herein describes the average shared genetic effect across the autosomes. It does not provide information pertaining to which regions of the genome (beyond the autosomal contributions) contribute to this effect. As such, it is of limited utility in understanding the shared biological systems (if any) that are linked to the observed genetic correlation. Additional work is required to identify regions of the genome that drive this genetic correlation.

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Author disclosures

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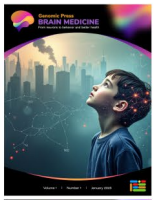

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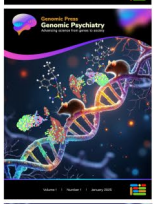

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