gp.genomicpress.com

Genomic Psychiatry

OPEN

EDITORIAL

From melancholia to molecular mechanisms: Bridging centuries of understanding depression

Genomic Psychiatry; https://doi.org/10.61373/gp025d.0101

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

Received: 1 October 2025. Accepted: 3 October 2025.
Published online: 21 October 2025.

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.

Julio Licinio[1], **and Ma-Li Wong**[2]
[1]*Editor-in-Chief, Genomic Press, New York, New York 10036, USA;* [2]*Genomic Press, New York, New York 10036, USA*
✉ *e-mail: julio.licinio@genomicpress.com and mali.wong@genomicpress.com*

References

1. Kendler KS, Justis V. The descriptive psychopathology of melancholia in Roubinovitch and Toulouse's 1897 monograph "La Mélancolie". Genomic Psychiatry. 2024:1–9. DOI: 10.61373/gp024i.0067.
2. Serretti A, Souery D, Kasper S, Bartova L, Zohar J, Montgomery S, et al. Polygenic liability to C-reactive protein defines immuno-metabolic depression phenotypes and influences antidepressant therapeutic outcomes. Genomic Psychiatry. 2025. DOI: 10.61373/gp025a.0098.
3. Penninx B, Lamers F, Jansen R, Berk M, Khandaker GM, De Picker L, et al. Immunometabolic depression: from concept to implementation. Lancet Reg Health Eur. 2025;48:101166. DOI: 10.1016/j.lanepe.2024.101166. PMID: 39801616; PMCID: PMC11721223
4. Fanelli G, Sokolowski M, Wasserman D, European College of Neuropsychopharmacology (ECNP) Network on Suicide Research and Prevention, Kasper S, et al. Polygenic risk scores for neuropsychiatric, inflammatory, and cardio-metabolic traits highlight possible genetic overlap with suicide attempt and treatment-emergent suicidal ideation. Am J Med Genet B Neuropsychiatr Genet. 2022;189(3-4):74–85. DOI: 10.1002/ajmg.b.32891. PMID: 35191176; PMCID: PMC9305542
5. Chavez-Castillo M, Nava M, Ortega A, Rojas M, Nunez V, Salazar J, et al. Depression as an immunometabolic disorder: exploring shared pharmacotherapeutics with cardiovascular disease. Curr Neuropharmacol. 2020;18(11):1138–1153. DOI: 10.2174/1570159X18666200413144401. PMID: 35191176; PMCID: PMC9305542
6. Sternberg EM, Licinio J. Overview of neuroimmune stress interactions. Implications for susceptibility to inflammatory disease. Ann N Y Acad Sci. 1995;771:364–371. DOI: 10.1111/j.1749-6632.1995.tb44695.x. PMID: 8597414
7. Wong ML, Dong C, Andreev V, Arcos-Burgos M, Licinio J. Prediction of susceptibility to major depression by a model of interactions of multiple functional genetic variants and environmental factors. Mol Psychiatry. 2012;17(6):624–33. DOI: 10.1038/mp.2012.13. PMID: 22449891; PMCID: PMC3359641
8. Licinio J, Frost P. The neuroimmune-endocrine axis: pathophysiological implications for the central nervous system cytokines and hypothalamus-pituitary-adrenal hormone dynamics. Braz J Med Biol Res. 2000;33(10):1141–8. DOI: 10.1590/s0100-879x2000001000003. PMID: 11004714
9. Licinio J, Wong ML. Digital footprints as a new translational approach for mental health care: a commentary. Discov Ment Health. 2023;3(1):5. DOI: 10.1007/s44192-023-00032-7. PMID: 37861744; PMCID: PMC10501006
10. Vreijling SR, Chin Fatt CR, Williams LM, Schatzberg AF, Usherwood T, Nemeroff CB, et al. Features of immunometabolic depression as predictors of antidepressant treatment outcomes: pooled analysis of four clinical trials. Br J Psychiatry. 2024;224(3):89–97. DOI: 10.1192/bjp.2023.148. PMID: 38130122; PMCID: PMC10884825

Publisher's note: Genomic Press maintains a position of impartiality and neutrality regarding territorial assertions represented in published materials and affiliations of institutional nature. As such, we will use the affiliations provided by the authors, without editing them. Such use simply reflects what the authors submitted to us and it does not indicate that Genomic Press supports any type of territorial assertions.