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Psychiatry is the flagship of personalized and precision medicine: proposing an epistemic horizon to biological psychiatry

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"Perhaps the history of errors of mankind, all things considered, is more valuable and interesting than that of their discoveries. Truth is uniform and narrow…but error is endlessly diversified." — Benjamin Franklin, from the *Report of the Royal Commission to Investigate Animal Magnetism*, 1784

In this editorial I use the advances in genetic studies of psychiatric disorders as a fulcrum to propose that there might be limitations on what we can achieve in biological psychiatry research; i.e., an epistemic horizon. I propose that more "digging" in biology might not solve the lack of biological validators of psychiatric disorders; rather we need a change in our conceptual framework of diagnosing and treating mental disorders. I propose that all that is needed to practise psychiatry and advance research in this field is to focus on "surface" phenotypes and their optimal treatment, using all the rich and diversified tools at our disposal. I believe this framework positions psychiatry as the flagship of personalized and precision medicine.

Since I started as co-editor in chief of the *Journal of Psychiatry and Neuroscience* (*JPN*) in 2010, working with Dr. Patricia Boksa and then Dr. Paul Albert until passing on this responsibility to Dr. Lena Palaniyappan, I have authored or co-authored 14 editorials, and I am grateful to all the editorial board members who reviewed, and often moderated, my views about practice and research in psychiatry. I also thank Dr. Albert for giving me the opportunity to write this "exit" editorial.

Using Google Scholar Citations as a metric to evaluate the impact of these editorials, 3 of the 14 stood out, with their number of citations surpassing 3 digits. These are the 3 editorials, by order of citations:

1. Publication bias: What are the challenges and can they be overcome?[1] (282 citations since 2012)
2. "Mental illness is like any other medical illness": a critical examination of the statement and its impact on patient care and society[2] (149 citations since 2015)
3. Mental wellness in Canada's Aboriginal communities: striving toward reconciliation[3] (113 citations since 2015)

Notably, these 3 editorials addressed major controversies and problems in the field, namely the replicability crisis in behavioural sciences[4–6] (and in biomedical sciences in general[7]), the difficulties our field faces in defining[8] and treating[9] mental illnesses, and the inequalities in service delivery in our societies and how these inequalities impact people with different ethnicities, genders and sexual orientations, geographical locations, socioeconomic status[10–14] and others. In the present editorial I update my views on the first 2 controversies and show how they may be connected. In addition, many of the 11 other editorials I contributed to *JPN* discussed some aspects of these 2 controversies. Notwithstanding the importance of the third one, and because of limited space and personal expertise in this field, I am not going to comment on it here.

Many commentators in the literature invoke a status of crisis in our discipline — a crisis based mostly on a few observations. First, except for the major psychotropic drugs that were discovered mostly by serendipity, few innovations have come from the billions of dollars spent on academic and pharmaceutical research.[15–17] Second, despite thousands of publications in the field of biological psychiatry, not a single biomarker has been validated to help diagnose major mental illness, and our nosology is still based on authoritative approaches more or less guided by the literature.[18] Third is the so-called treatment–prevalence paradox; i.e., the persistence of a high prevalence of mental disorders in the general population despite major efforts to reduce that prevalence.[19,20]

The crisis is reflected in the opening sentences of our grant applications, in the introduction sections of our manuscripts, and in our presentations where we tend to convey the idea that nothing or very little is known about psychiatric disorders and that everything needs to be invented. The student of medicine is often left with the impression that psychiatry is at the stage of development where cardiology was before the

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discovery of stethoscopy or nephrology before the age of kidney biopsy. Strong proponents of biological psychiatry believe that the equivalent of these tools — brain imaging, genetic testing, and a myriad of other biomarkers — need to be found to allow psychiatry to achieve the level of development attained by other medical specialties, and critics will ask how long we should wait before we call biological psychiatry a failure and quit altogether. After all, more than 200 years have passed since Wilhelm Griesinger declared that "all mental illnesses are cerebral illnesses," and yet no strong (in the sense of diagnostic test) or even weak (in the sense of consistently replicable/useful correlation) association has been established between the brain and any of the major mental illnesses (except for Alzheimer disease, which has clear brain pathology, and may be considered a neurologic condition).

I will argue that, contrary to these views, psychiatry is in fact the flagship of personalized and precision medicine, but a conceptual change of how we interpret the last 50 years of research in the field of biological psychiatry is needed.

The replicability crisis

When I started my residency and research career, I was fascinated by the genetics of mental disorders, mainly because of the very solid data showing that most psychiatric disorders have very high heritability (h^2). These results were based mostly on twin studies, a unique natural experiment using pairs of monozygotic (MZ) and dizygotic (DZ) twins. Notwithstanding some complexities of the model, one can estimate how much the entire genome contributes to variation in psychiatric phenotypes, just by comparing the concordance (C) in MZ and DZ twins using a very simple formula: $h^2 = 2(C_{MZ} - C_{DZ})$. This field of research achieved very robust findings, consistently reporting high heritability of all major psychiatric disorders using relatively modest sample sizes.[21–24] There is no replicability crisis in this domain.

An important question to ask is why this field of research did not suffer a replication crisis. My answer would be that the field has a few epistemic specificities that make it stand out from all the other research domains in psychiatry. By epistemic specificities, I mean characteristics that are unique to this field, as compared with general epistemic characteristics that ground knowledge and make it possible in general. These specificities are as follows:

- The independent variable (sharing 100% or 50% of genes between siblings, or having a specific genetic variant in any locus) is discrete and very reliably measurable.
- Because of the clarity of this independent variable (zygosity status or genetic variant), studies from all over the world can be assembled with very minimal errors (at least regarding the independent variable), and statistical power can be improved at will.
- A very large number of DNA samples can be stored in 1 fridge for hundreds of years and be queried in millions of loci whenever need be.
- Causality is readily interpretable. Genes affect phenotypes; phenotypes do not affect gene DNA sequence. This contrasts with all nongenetic studies, where the interpretation of causality is often confounded. This in fact is even the case for epigenetic studies where the independent variable (e.g., CpG methylation) is slightly removed from genes.

I believe these specificities are the basis of the robustness of this field of research; i.e., its capacity to yield very firm conclusions. I also believe that no other field of research in biological psychiatry has such robust epistemic specificities.

In addition to this solid heritability, the mid-1980s ushered in a revolution in medical genetics based on reverse gene mapping of diseases[25]; one just needs DNA samples from a few members of families segregating a disease to map and identify the culprit gene/mutations causing that disease. The first human disease that was causally resolved using this approach was Huntington disease.[26] A few years later, 2 studies heralding the mapping of genes with major effects for schizophrenia[27,28] and bipolar disorders[29] were published in prestigious journals. It is in that context that I started my PhD studies on the genetics of schizophrenia in 1993 at McGill University with Drs. Benkelfat and Rouleau. Owing to my interest in improving pharmacotherapy, I was compelled to conduct pharmacogenetic studies under the premises that we know a lot about the mechanisms of action of psychotropic drugs (e.g., modulation of dopamine, serotonin), that we can measure pharmacogenetic phenotypes using the gold standard methodology in medicine (randomized double-blind clinical trials), and that functional genetic variants in genes coding for proteins involved in neurotransmission pathways relevant for pharmacogenetic phenotypes are available. In addition to these solid experimental characteristics, the field appeared to me the closest to precision medicine; results can be readily translated from the laboratory to the bedside. I had the impression that we were on the cusp of major discoveries based on strong hypothesis-driven research.

However, with time the number of genetic association studies, including studies by our group, skyrocketed and replications were a major problem.[30–33] The more sample sizes increased, the less likely it was to replicate their findings, contributing to an exacerbation of the replicability crisis. This was also the case for linkage studies, where many high-profile findings were published in prestigious journals only to fade afterwards.[34]

It was that state of affairs that led to me writing the editorial, "Publication bias: What are the challenges and can they be overcome?," with Drs. Boksa, Annable and Schmitz.[3] The basic message was that the majority of studies in psychiatry are statistically underpowered, leading to a flood of false-positive results. The direct implication for *JPN* was that we decided to reject studies with relatively small sample sizes, and we encouraged submission of studies with negative results when they were based on sound designs and had reasonable statistical power.

I will argue here that the epistemic robustness of genetic studies is the main factor that helped the field of biological research to appreciate the depth of the replicability crisis and understand its causes. I also propose that a correct interpretation of this crisis will probably help to develop a new conceptual framework for research in psychiatry.

After the crisis of replicability related to genetic linkage and association studies, investigators from all over the world formed consortia where DNA samples were assembled to conduct genome-wide association studies (GWAS).[35] The initial studies[36] included relatively modest sample sizes (a few hundred) and reached much larger numbers in the last few years (a few thousand).[37,38] These studies led to highly reproducible results like those in the twin studies. Moreover, these GWAS did not find any association with the genes that were reputed to play some role in the etiology of psychiatric disorders,[39] indicating that all our previous biological knowledge about these disorders did not help to formulate sound hypotheses. What helped the field reach this high level of consistency was the use of very large sample sizes and not relying on any prior biological knowledge. I believe that our incapacity to formulate sound hypotheses based on decades of biological research and the need for very large sample sizes to identify genetic variants consistently associated with psychiatric disorders represent the true measure of the depth of the replicability crisis. I also believe that, if this is the case in a field where research has robust epistemic specificity, fields where these specificities are absent or weaker (most of biological psychiatry), the crisis might be even deeper (although not necessarily apparent).

The biological causes of the replicability crisis lay in the complexity of the genetic architecture of these phenotypes. Without going into the intricacies of this complexity[40,41] (e.g., common variant v. rare variants v. copy number variants), GWAS identified hundreds of single nucleotide polymorphisms (SNPs) with very small effect sizes that are distributed all over the genome and, in the majority of cases, not located in coding regions of genes. This clearly reveals the main cause, from a biological point of view, of the replicability crisis (there are also sociological determinants of this crisis that will not be discussed here[42–45]): the extraordinary complexity of the genetic architecture of psychiatric disorders. While the twin studies that have captured the effect of the whole genome on a given disorder have been successful using a few hundred twin pairs, finding the genetic variants and the biological mechanisms linking genes to behaviour is a much more complex task.

In the next section, I will discuss this complexity and try to reflect on the implications for biological research.

I believe it is important to discuss how we can interpret these findings to move the field ahead. Should we say that we have pushed biological research to its limits, using robust methodology, and we ended up having "dusty" effects that we cannot translate in any useful way into the clinical arena,[46–48] or should we keep digging until we find the missing links between psychiatric disorders and some actionable biological abnormalities in the brain? I have no doubt that the biologically oriented researchers will adopt the latter strategy. After all, who can be against the pursuits of incremental progress?[49] In addition, whole psychiatric departments, professionals, journals and others have a clear interest to keep this going,[50] but I believe that there is also some value in arguing otherwise: GWAS indicate that there is some kind of epistemological horizon — a fundamental limit to the knowledge that we can obtain about a system — that is difficult to surpass.

This concept of the epistemic horizon has been introduced recently as one of the principles grounding many of the limitations in knowledge that are part of basic sciences (e.g., logic, computation).[51–53] Even in hard sciences (e.g., math, physics), there is a limit to what we can achieve using a deterministic framework. For example, the program of Hilbert to ground all mathematics on the basis of axioms and their consistency failed when Gödel proved that even simple mathematical systems, such as arithmetic, could not be completely and consistently constructed based on axioms and logic alone.[54] In physics, it has been very clearly shown that randomness is a fundamental phenomenon and our knowledge of the world is always embedded in some fundamental and irreducible randomness.[55] It is thus quite possible that in the field of psychiatry and neuroscience there are limitations to how far we can push mechanistic knowledge. In a previous editorial, I discussed how randomness can play a role at different levels of analyses in psychiatry.[56] Of course, some will say that these are philosophical speculations with no bearing on our field and that we just need to keep digging. However, I will argue that, even if they do not amount to a formal demonstration like in math and physics, they strongly suggest that our mechanistic knowledge is bound by some epistemic horizons that we need to keep in mind when we are interpreting our field of research.

To illustrate this, I will briefly discuss a major GWAS on the genetic determinants of height, a very "simple" trait, that was published recently.[57] The authors included 5.4 million individuals to identify 12 111 independent SNPs that are significantly associated with height and account for nearly all the SNP-based heritability; i.e., they identified a saturated map. More importantly, they also showed that all this dense genetic information does not outperform basic family data in predicting a person's height. Indeed, prediction accuracy based on SNP data was 40% and prediction accuracy based on parental average was 43.8%. There is a major message that we can derive from this GWAS in relation to a very simple trait (simple from a measurement point of view, although this trait may be very complex[58]): a very large proportion of the genome and of genetic variants is implicated in explaining the variance of this simple trait and, most importantly, measuring the average height of parents is a very good predictor of the height of an individual, as accurate as these vast molecular data. In other words, a "surface" phenotype (parent's average height) may tell us a lot about the phenotype of an individual of interest.

Now, extrapolating to our complex phenotypes (e.g., schizophrenia, bipolar illness), each of these is a very complex construct of, in turn, many complex constructs (e.g., attention, perception, volition, emotion abnormalities, social defeat, guilt, trauma), and all of these are assessed, at best, via some validated scales. We may ask, what will the sample size be that will saturate the SNP map for any of these disorders, and how many SNPs would we detect at the end of this journey? I would answer, probably hundreds of millions of patients and all the SNPs of the human genome. I might be wrong about the rough estimates, but in any case, and if the study of height is a guide, all the biological data that would

come from these studies would not outperform our surface phenotyping such as parental mid-phenotypes or MZ co-twin phenotypes.

Next, I will present the arguments that a biologically enthusiastic researcher may present in favour of continued digging in the search for biomarkers, and will try to point to some limitations of these arguments.

It may be argued that, once we obtain a saturated SNP map for any of the psychiatric disorders, we can then perform molecular pathway analyses, determine the relevant molecular circuits, identify the different developmental brain abnormalities (molecular, cellular or structural) until we connect with the higher level of endophenotypes such as neuropsychological or other brain abnormalities (as measured using different imaging techniques) and finally identify the causal pathways connecting the SNP map to the complex mental disorders. While it is possible to gain some biological insights from such bottom–up approaches, it is important to note that any investigation leveraging biological insights gained via genomic information will not have the epistemological robustness of genetic studies. Measurements of any phenotype/endophenotype bracketed between the genetic factors and our phenotypes of interest may be much less reliable and confounded by environmental and other factors, and the circularity in causality will be impossible to factor out. It is also very likely that the effect sizes that these studies will be chasing are very small and that large enough sample sizes are very hard to assemble. Such conditions are the exact prescription for the replicability crisis.[59]

Another line of reasoning is that maybe we can use biological insight gained from genomic information to design molecules that interfere with biologically relevant pathways and transform these molecules into drugs that will help cure the diseases of interest. Here again, examples of success using this approach are extremely rare. For example, consider Huntington disease, caused by a single major mutation identified 40 years ago: no novel pharmacological intervention has been identified in this field, and the treatment of chorea still relies on antipsychotic medications that were in use before the discovery of the Huntington gene.[60] We can imagine that it might take an eternity to accomplish pharmaceutical discoveries in disorders where the gene effects are tiny and the biology is very complicated. A notable exception though (maybe the one that proves the rule) is the development of orexin antagonists for the treatment of insomnia.[61] In addition, historically, almost all of the drugs used in psychiatry were discovered serendipitously by observing behavioural effects when these molecules had been given to humans for other purposes. These clinical observations gave us our first major treatments and initiated a rich field of psychopharmacology research that led to a large number of medications via targeted medicinal chemistry (including pharmacological approaches to substance use disorders). This gave us a pharmacopeia as rich (if not richer) and effective as most of the pharmacopeia in other chronic human diseases.[62,63] In another editorial, I argued that the crisis in biological psychiatry is not due to lack of findings, but rather to our failure to act on what we already know.[64] For example, a glaring collective failure in our practice of psychopharmacology is the perennial underuse of clozapine in the treatment of resistant schizophrenia.[65] I also believe that our care systems need an overhaul to best implement the therapeutic recommendations,[66,67] which may solve, at least in part, the treatment–prevalence paradox.[19,20] Continuing a pursuit of molecules with questionable marginal benefits[15–17] may in fact syphon much needed resources for patient-oriented research.[68]

The final argument that the biologically enthusiastic researcher may use is that gene–environment interaction can help to identify the environmental factors that can be used to improve our understanding of the causality chain, and develop prevention strategies and even therapeutic interventions. A paradigmatic example is the case of phenylketonuria (PKU) mental retardation. The discovery of the genetic anomaly permitted a complete cure of the condition by eliminating exposure to phenylalanine. However, here again it is important to remind the reader that the replicability crisis is major in the field of gene–environment interactions.[69] Sample sizes are often small or very small; the measurement of environmental risk factors is fraught with errors and lack of reliability, especially when these factors are present in the early developmental periods of the patient's life; and, contrary to discrete genetic risk factors (variant is present or not), environmental risk factors are not naturally segmented and are often estimated via proxy measures (e.g., socioeconomic status is measured via a combination of salary, education and other factors). In addition, one of the major problems in this field is that causality is hard to establish. Recently, a method called Mendelian randomization has been developed to improve causality imputation of environmental factors. For example, Choi and colleagues[70] conducted a Mendelian randomization over 106 modifiable factors (e.g., lifestyle, social support, contaminants) based on GWAS data from more than 100 000 participants from the UK Biobank with depressive traits. While many of these risk factors were associated with depression, only 2 were validated as having a putative causal relation with depression (confiding in others is protective, and television use is risk related).[70] While these kinds of studies can give some insights, much larger sample sizes and prospective measurements of risk factors will be needed to reach the level of statistical robustness offered by GWAS studies.

I propose that genetic studies revolutionized the field of biological psychiatry, not so much by identifying actionable factors, but mostly by showing that the biological underpinning of psychiatric disorders is extremely complex and by putting a limit on how much deeper we can dig in biological research — a sort of epistemic horizon described in other fields of science. This was possible because of the robust epistemic characteristics of genetic research that appear to me very hard if at all possible to match by any other field of biological research in psychiatry (although brain imaging research is forming consortia and trying to overcome its own replication crisis[71–74]). I think that this field does not have the robustness of genetic research, and it will be interesting to follow the longer term outcome of this line of research. Another important conclusion from this research is that surface phenotypes are very important tools for the prediction of complex phenotypes, and they

may be even more fundamental in the field of psychiatry. By surface phenotypes, I mean all the information that the patients confide in us, and the data that we can collect via our clinical observations. Digging deeper into biology to understand these surface phenotypes may be unnecessary, impossible to advance, and probably counterproductive for research and care in psychiatry. In brief, psychiatric disorders are fundamentally genetically determined, but genes do not matter in our day-to-day practice. The interpretations discussed here lead me to believe that psychiatric disorders are also fundamentally brain disorders, but brains do not matter when we are practising psychiatry. The replicability crisis can be solved using a new interpretation of our findings: yes, genes and the brain are fundamental (how can they not be?), but the genetic/brain mechanics (including all the layers between genes and surface phenotypes) are mostly insolvable because they are marred in very high levels of complexity.

This leads me to discuss the second editorial, titled "'Mental illness is like any other medical illness': a critical examination of the statement and its impact on patient care and society,"[2] which I co-authored with Drs. Malla and Garcia.

The nosology crisis

In the above-mentioned editorial, we tried to dissect the contention and implication of the often used expression, "mental illness is like any other medical illness," reaching the conclusion that equating mental illness with medical illness, situating it in the brain and using brain–behaviour correlations, cannot be justified on the basis of the current state of knowledge. More fundamentally, not recognizing the relevant locus of mental illness — the whole person, the "self" — will not serve our patients and society. The arguments supporting this view are well developed in that editorial, but I will focus here on the debate surrounding the nosology crisis; i.e., the fact that psychiatric nosology lacks validation.

The *DSM* movement was based on the need to deal with the problem of reliability of diagnosis first, and the idea that the problem of validity would be solved with future advances in research.[75,76] As a medical student, I was trained in the strong medical model using all the tools (e.g., collections of signs and symptoms, radiology, laboratory tests, electrophysiology) to diagnose disorders. The publication of *DSM III* and its premises were another fascination to me, and my medical dissertation was on *DSM III* and its use in Tunisia (under the supervision of Prof. T. Skhiri). Again, like most of the people working in the field of biological psychiatry, I was convinced that by using a common, reliable language we were on the cusp of major discoveries. This seemed particularly possible, as I was extremely fortunate to live through the decade of the human genome[77] and the decade of the brain.[78] However, decades passed and considerable work in biological psychiatry was dedicated to the validation of these diagnostic entities, but not a single biological validation was made (except for a molecular marker for narcolepsy). Many of the major actors in this field of research tried different approaches to solve this vexing problem.[79] In another editorial, titled "On the simple and the complex in psychiatry, with reference to *DSM 5* and research domain criteria,"[58] (RDoC) I discussed some of the main ideas that have been advanced in the *DSM 5* and RDoC initiatives to help the field identify biomarkers and solve the validity crisis. Both discussed the idea of using simpler/measurable constructs: behavioural in the case of *DSM 5*, and biological in the case of RDoC. Based on simple genetic epidemiological arguments, I defended the idea that the debate about what is simple/complex (e.g hallucination/schizophrenia) is deceptive and misleading. Many of the assumptions about traits that we intuitively conceive of as simpler/measurable than the complex disorders (e.g., sadness may be simpler than major depressive syndrome) may not be true. Again, consider the paradigmatic example of the genetics of height:[57] as discussed, the genetic architecture of this presumably simple trait is extremely complex, but many dwarfism syndromes (where small height is part of a complex syndrome) may have a much simpler genetic architecture, possibly only a single or a few mutations.[80]

Consequently, I propose that the validity crisis should be solved by stopping our pursuit of this illusion. There might not be biological validators of mental disorders, and nosological science should pursue other avenues, such as considering surface phenotypes the major object of research for and by themselves. By doing so, we may recuperate an extraordinary wealth of clinical phenomena that were developed over 200 years of phenomenological research but completely lost in our list-oriented diagnostic criteria. In an editorial titled, "From the neo-Kraepelinian framework to the new mechanical philosophy of psychiatry: regaining common sense,"[81] I presented some examples of these clinical symptoms (e.g., psychotic ambivalence, delusional mood) that need to be reintroduced, to be carefully taught to the new generation of clinicians and hopefully create a better clinical framework for increased empathy and better clinical care. In fact, important new frameworks of research in nosology are emerging and may enrich this debate. For example, the Hierarchical Taxonomy of Psychopathology (HiTOP) paradigm uses the observed covariance of dimensional traits and factor analysis techniques to identify a hierarchy of hidden factors that improve our understating of signs and symptoms.[82,83] On top of this hierarchy a general psychopathology "p" factor is postulated, with many hidden layers of subfactors. The main premise of this framework is that since psychopathology is dimensional (e.g., neuroticism, externalizing, internalizing, thought disorders), nosology should also keep away from categories and adopt a dimensional approach. In line with the previous nosological frameworks, HiTOP proponents argue that this model is consistent with evidence on risk factors, biomarkers, treatment response and course of illness.

More recently, a new framework for nosological research adopted surface phenomenology as its main focus. Signs and symptoms are considered the basic unit of analysis, and there is nothing deeper that needs to be understood to have a functional nosology. This approach is called network analysis, and it seeks to understand how signs and symptoms (nodes of the network) are related to each other and form a network, the dynamic of which should be the object of this research program.[84] It postulates that psychiatric disorders are problems of living and, as such, need to be understood at the level of what is observed as

expression of human suffering: sadness, guilt, shame, fear, hearing voices, feeling defeated, and others. Psychiatric disorders are best understood at this level rather than by invoking underlying causal factors. These symptoms (e.g., sadness), once triggered by some factors (e.g., the death of a loved one), can activate and synchronize with some other symptoms in their network (e.g., guilt), and this pair of symptoms can reinforce each other until they form a stable system and can spread to other related nodes in the network and form a constellation departing form the normal state, which represents the disorder. While there is now an active effort to advance this approach empirically, and much needs to be done to enrich this approach and show its utility, I find it very attractive by its attachment to the surface phenomenology and the explicit rejection of the need for deeper explanations. This is in line with what I tried to defend in the first section of this editorial.

Finally, remote sensing and collection of behavioural data via portable devices is emerging and may enrich the field of surface phenotyping. Indeed, with the tremendous advances in technology and artificial intelligence, collection of surface phenotypes that have been previously difficult to collect continuously over time (e.g., sleep, speech, psychomotor characteristics) are becoming easier to collect and interpret, which might improve our diagnostic and therapeutic approaches.[85]

I believe that this approach to nosology/semiology puts the person at the centre of our focus: we need to engage with and listen to the person, explore the extent of their suffering, and provide the help using the whole span of interventions that the person needs. Of course, in this work, understanding the patient's personal history, embedded in the family, social and even universal context, is fundamental. This understanding is always dynamic, and needs to be constructed as a continuous dialogue with the patient, meaning that no diagnosis (in the medical sense) can ever definitely pigeonhole the patient. In practising this hermeneutic approach,[86] not only can our patients be healed, but we also, as care providers, may transform our understanding of our personal history and ourselves, as may be inferred from the discussion in this editorial about my personal journey in biology and psychiatry.

Conclusion

The main thrust of this editorial is to show that the field of psychiatric genetics has contributed tremendously to research in psychiatry, not so much by validating any disease entity, but by showing the complexity of the biological mechanisms of these disorders and that these underpinnings may be impossible to identify. While it is impossible to demonstrate that this is a final conclusion (and I hope that I will be contradicted tomorrow), I argue that the epistemic robustness of genetic studies combined with the very complex but trivial "findings" in this field clearly define the epistemic horizon in biological psychiatry. If so, a paradigmatic shift is necessary in psychiatry. This paradigmatic shift stipulates that when a patient presents with problems of living and confides in us a rich phenomenological experience that we can help them to interpret, understand and eventually resolve, there is no need to seek biological explanations that are at best trivial and at worst unattainable. Surface phenotypes are all that we need. More than any other medical discipline, psychiatry offers a rich variety of tools to help patients recover: pharmacotherapy, various psychotherapy techniques, and a wide range of psychosocial/holistic help. In this sense, I think that psychiatry is the flagship of precision and individualized medicine, and not the archaic discipline that we often tend to depict in our grants, papers and presentations. In fact, it may be that the rest of medicine needs to emulate some components of this model rather than psychiatry trying to carve out a place within the medical disciplines.

Finally, I strongly believe that behavioural neuroscience (both in humans and animals) has contributed remarkably to our understanding of human cognitions, motivations and actions, and will be always one of the facets we use to interpret (not explain) signs and symptoms a given patient presents to us. As such, behavioural neuroscience will remain part of the hermeneutic toolkit to help us understand the enigma of health and disease.[87] However, I believe that we need to refrain from conducting behavioural neuroscience research under the guise of biological psychiatry. A PubMed search for "biological cardiology" (to take an example used earlier), yielded 0 publications. By contrast, searching for "biological psychiatry" yielded 17 207 entries. It goes without saying that most medical disciplines are biological in nature, and the expression "biological cardiology" may be considered vacuous. Based on biological arguments and the recent history of the field, I offer in this editorial a framework in which the expression "biological psychiatry" can be considered vacuous as well. Psychiatry has profound but remote biological/brain roots. It should operate at much higher levels of analysis.

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