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Invited Letter Rejoinder

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Misunderstanding precision psychiatry

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We thank van Os and Kohne for their reply to our commentary. It is true, we are in love with the concept of precision psychiatry. But we are not blindly in love. Our love for precision psychiatry is based on remarkable and rapid advances in biological psychiatry – closely linked to advances in technology – that support the potential of this paradigm shift. Some of these advances were presented in our previous commentary (Salagre & Vieta, 2021). Yet, van Os and Kohne question the foundations of precision psychiatry. And, by doing so, they question the very foundations of current psychiatric practice and how we understand mental processes.

The mind–brain paradigm

van Os and Kohne indirectly raise the question of the mind–brain paradigm, as they express their concern 'if, how and to what degree mental phenomena are represented physically'. Although Descartes body–mind dualism postulated a world of material things and immaterial minds, the contemporary belief is that world is material, and that mental states cannot occur independently of physical processes. From a scientific perspective, there is evidence that psychotropic drugs or inflammatory processes like anti-N-methyl-d-aspartate (NMDA) encephalitis can produce symptoms (such as hallucinations or delusional thoughts) that are indistinguishable from those observed in severe mental disorders by acting on something 'physical', that is, receptors in the brain. It seems reasonable to assume, then, that the identical symptoms observed in psychiatric disorders might also arise from an alteration in brain functions. We are dealing with the more complex and enigmatic organ in the body, which poses a challenge to the discovery of the best methodology to study the underlying processes that lead to altered mental states. But these processes exist regardless of whether we can understand them. Just as NMDA encephalitis existed before it was described, nearly 15 years ago (Dalmau et al., 2019). Therefore, if other organs in the body have benefited from precision medicine, why would not also the brain, once the methodological barriers are overcome?

Luckily enough, though, the mind–brain problem does not need to be solved to advance in precision psychiatry. Pharmacogenetics (Vilches, Tuson, Vieta, Álvarez, & Espadaler, 2019), behavioral biomarkers (Scott, Hennion, Meyrel, Bellivier, & Etain, 2020) or mHealth (Hidalgo-Mazzei et al., 2018), for instance, are areas of precision psychiatry that do not rely on deciphering the biology of mental disorders and still can lead to more precise and personalized treatments.

Mental disorder *vs.* mental suffering

In their reply, van Os and Kohne seem to reduce the essence of mental disorders to acute mental distress. But, does mental suffering alone reflect the complexity of psychiatric disorders?

As Guze (Guze, 1978) exposed in 1978, psychiatry is a branch of medicine and, as such, its focus expands beyond acute suffering since it deals with the causation, prevention, diagnosis and treatment of mental and behavioral disorders. It needs to pay attention to the biological underpinnings of mental disorders and the study of environmental risk factors (to achieve stable and value-free scientific definitions of mental disorders) as much as it needs to care about the emotional and social impact of these disorders. It is quite unfair to claim that precision psychiatry may disregard the person as a whole and the important input of patients and sufferers. Research on the functional impact of mental disorders is as important as biomarkers and clinical trials (Valls et al., 2020). Having said so, issues such as the fight against stigma may be successfully addressed by solving the problem with the scientific method: curing the disease. What is the stigma associated with smallpox nowadays?

Finding 'biomarkers of human emotions' is not the goal

Again, in their arguments, van Os and Kohne seem to misinterpret the foundation of precision psychiatry by arguing against 'biomarkers of human emotions', confounding illness

biomarkers with hypothetical biological correlates of physiological brain processes, such as emotions. This is not about precision psychology, it is about understanding the underlying causes of the disorders of the brain that fall under the umbrella of 'Psychiatry', which, by the way, included, in the past, infectious diseases such as 'Progressive Paralysis' (caused by *Treponema pallidum*) and neurodegenerative conditions like Alzheimer disease (now part of what we call 'Neurology', given that we have partially ascertained their pathophysiology).

Similarly, by performing studies at the group level with multiple levels of information, machine learning methods can help to detect which biological and environmental factors are more related to – for instance – experiencing a depressive relapse (not only sorrow, which, again, is a psychological concept) after the loss of a loved one, to use the same example as van Os and Kohne, and then help to establish a probability at the individual level (Lahey, Moore, Kaczkurkin, & Zald, 2021). Of course, as in any predictive model, results are neither immutable nor perfect, but as the elements of the model change, so will change the probability. Just as the predictions in weather forecasting, which also deal with chaos theory, are not always accurate. But the real question is: will machine learning models, combined with clinical expertise, lead to more accurate predictions than clinical expertise alone? That is what needs to be solved, and what current research is working on, with some success.

Conclusion

The foundations of precision psychiatry are solidly anchored on the scientific method (Manchia et al., 2020). While it is true that psychiatric conditions are currently defined as 'syndromes', like *fever* in the context of internal medicine, and thus lack the validity and specificity of infectious diseases, for example, it is also true that fever is most often caused by an underlying illness, with a verifiable biological background. The brain, like any other organ of our body, can get sick. Hence, the medical model, represented by the modern concept of 'precision psychiatry', seems to us the way forward to understand the complex phenotypes that mental disorders represent, achieve more objective definitions of mental disorders and improve current treatments to alleviate mental suffering more effectively. Importantly, 'biology' and 'humanity' are not mutually exclusive concepts, and biology is not deterministic. We hope that in the future precision and humane treatment will go hand in hand to offer the best medical care to the patient as a person, bridging the gap between precision psychiatry and person-centered care. This should be the essence of personalized psychiatry.

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