VIEWPOINT

Are Psychiatric Disorders Brain Diseases?—A New Look at an Old Question

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Modern biological psychiatry began with these words from the influential mid-19th century German psychiatrist Wilhelm Griesinger "The first step toward a knowledge of the symptoms [of insanity] is their locality—to which organ do the indications of the disease belong? … Physiological and pathological factors show us that this organ can only be the brain."[1]

Since then, there has hardly been a more vexed question in our field than "Are psychiatric disorders brain diseases?[2]" I hope to clarify the issues involved and provide a way forward on this question.

Two potential answers are nonstarters. The first is a philosophical argument. If we reject Cartesian dualism, which posits that the mind is an entirely different kind of stuff than the brain, this can lead to the commonly adopted philosophical position on the mind-body problem called *emergent materialism*. This Viewpoint posits that the mind emerges from and is instantiated within the brain. Although exactly how this works remains uncertain, one corollary is that no mental experiences occur without a brain. Since psychiatric disorders are largely defined by mental phenomena, ergo, they must be brain disorders. This argument is not helpful. All mental experiences—normal and psychopathological—are equally brained. Declaring disorder X to be a brain disease is uninformative.

Second, the field of psychiatry has evolved on a specific historical arc. Eighteenth century mad doctors sought to constitute a medical discipline treating insanity with a focus on the brain, although little was known about its function. A century later, with advancing methods of gross and microscopic neuropathology, disorders that presented with mental/behavioral disturbances associated with detectable pathology in the brain (eg, tumors, strokes, traumatic injuries, prominent neurodegeneration) were assigned to the nascent field of neurology, which studied brain disorders and, thereby, were excluded from psychiatry. In defining the relationship of psychiatric disorders to brain disease, we need to move beyond this classical definition that ignores disease processes operating only at physiological or molecular levels. Indeed, 20th century antipsychiatrists attacked the validity of our discipline, using this outmoded concept of brain disease. Neuroscience has advanced too far since then for us to be tied to this 19th century view, as witnessed by impressive recent advances in mapping the mammalian brain through advanced cellular transcriptomics.[3]

Can we develop a new approach to this problem that relies neither on philosophical argumentation or outdated definitions of brain disorder? I think so, with one caveat. We have to turn from the philosophical requirement that we define, at a fundamental level, the nature of the relationship between psychiatric disorders and brain disease, and turn instead to a more modest but more tractable question—can we show that critical causal pathways to psychiatric illness occur in the brain?

To proceed, I use the most robust empirical findings in all of psychiatry—that genetic risk factors impact causally and substantially on liability to all major psychiatric disorders.[4] I capture this relationship in a simple causal diagram: risk genes → psychiatric disorder. The test I propose is one of mediation. Can we determine whether the brain sits in this causal pathway like this: risk genes → brain → psychiatric disorder?

This question is addressable because a substantial proportion of human genes are expressed only in specific tissues, and for a goodly number, only in the brain. Recent decades have seen the emergence of a novel technology for measuring the level of messenger RNA expression in tissues and then demonstrating their association with DNA variation.

Our paradigmatic example is the 2022 report of a Genome Wide Association Study of schizophrenia from the Psychiatric Genomic Consortium Schizophrenia Workgroup.[5] In that article, they examine the association between many discovered schizophrenia risk variants and the expression of the relevant genes in 37 human tissues. Significant elevations are seen in 11 tissues, all reflecting different brain regions and specifically neurons. That is, no statistical elevation in expression of schizophrenia-risk genes was seen in any other part of the human body except the brain. These results provide strong support for the hypothesis that a substantial proportion of the genetic risk for schizophrenia results from the expression of these genes in brain, that is: schizophrenia risk genes → brain → schizophrenia. Does this mean that we can now declare that schizophrenia is a brain disease? Not in the old 19th century sense. But we can make the more modest claim that the effect of the strongest known risk factor for schizophrenia—genetics—largely occurs in brain tissue. Other results pointing in this direction are emerging from related methods applied to major depression and bipolar disorder.

While this claim might be less satisfying than the firm pronouncement that schizophrenia is a brain disease, let me suggest 5 advantages of this approach. First, it is not a metaphysical claim, but one based in data. It can be challenged and some variation in results expected. For example, a meaningful proportion of the genetic risk variants for alcohol use disorder are not expressed in brain, but rather in liver and gastrointestinal tissues[6] and evidence is emerging that genetic risk for eating disorders may be partly mediated by metabolic processes. So, the brainedess of our major disorders may be variable, at

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least from a genetic perspective. Second, it avoids the thorny conceptual problems, such as the lack of gross pathological brain changes in schizophrenia that are associated with real brain disease using the 19th century concept. Third, this approach fits easily into a pluralistic causal framework and would be consistent with the importance of other etiological pathways for psychiatric illness, such as social-environmental factors. Fourth, it can be informative about disorders outside our nosologic frame. For example, a number of key risk genes for obesity are primarily expressed in the brain.[7] What might we see for other syndromes, such as fibromyalgia or irritable bowel syndrome? Fifth, this approach sidesteps the problematic question of how to distinguish, at the level of brain physiology, normal variation from disease. Rather, we use genetic studies, and the differences in genetic variation seen between cases and controls, to detect the relevant gene expression differences.

This model has 1 important limitation—it is entirely genetically focused. That is for 2 reasons. First, variation in genomic DNA is causally privileged because of our biology. Genetic variants can influence disease risk but not the other way around. Second, we now have more powerful methods to detect tissue level expression of genetic risk than we do of other, eg, environmental, risk factors. So, this approach should be seen as a start and not a conclusion of an approach to determine, based on scientific findings, the degree to which the key physiological substrates for psychiatric illness occur in the brain.

In conclusion, the question of whether psychiatric disorders are brain diseases cannot be answered definitively as a metaphysical problem using philosophical tools. If we stick to the old 19th century model of brain disease, we are, I argue, asking the wrong question. Our way forward is to convert this question into a scientifically tractable form, which I try to do here by asking where in the human body genetic risk factors for our disorders are expressed. A tentative answer, at least for schizophrenia, would have pleased Griesinger: "it is entirely in the brain."[1]

ARTICLE INFORMATION

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REFERENCES

1. Griesinger W. *Mental Pathology and Therapeutics*. The New Sydenham Society; 1867.

2. Jefferson A. *Are mental disorders brain disorders?* Routledge; 2022. doi:10.4324/9780367822088

3. Yao Z, van Velthoven CTJ, Kunst M, et al. A high-resolution transcriptomic and spatial atlas of cell types in the whole mouse brain. *Nature*. 2023;624(7991):317-332. doi:10.1038/s41586-023-06812-z

4. Flint J, Greenspan RJ, Kendler KS. *How Genes Influence Behavior 2e*. Oxford University Press; 2020.

5. Trubetskoy V, Pardiñas AF, Qi T, et al; Indonesia Schizophrenia Consortium; PsychENCODE; Psychosis Endophenotypes International Consortium; SynGO Consortium; Schizophrenia Working Group of the Psychiatric Genomics Consortium. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*. 2022;604(7906):502-508. doi:10.1038/s41586-022-04434-5

6. Zhou H, Sealock JM, Sanchez-Roige S, et al. Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nat Neurosci*. 2020;23(7):809-818. doi:10.1038/s41593-020-0643-5

7. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. *Nat Rev Genet*. 2022;23(2):120-133. doi:10.1038/s41576-021-00414-z