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Invited Commentary

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Are neurotransmitters passé? A view from the foothills in response to Rose

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Professor Rose acknowledges disarmingly that he states the 'blindingly obvious' and we can only agree with his comments on the complexity of the brain, the heterogeneity of the depressive experience, its embodied nature, and socio-cultural location. Nevertheless, for clinicians trying to help seriously depressed people, the Olympian view is not always available, and a pragmatic approach may be needed. In this context, we believe that central neurotransmitters remain important, both in understanding the pathophysiology of mental experience, as well as the effects of currently available pharmacological treatments.

At this point, it is worth noting that even though a clinical syndrome may have heterogenous manifestations, this does not logically entail an equal number of causations or necessarily an indication for multiple treatments. Vitamin deficiencies are an obvious example of this. The simple technique of tryptophan depletion can cause a clinical relapse of the individual depressive syndrome in people recovered from depression and off medication for long periods of time. Thus, in some vulnerable individuals, lowering serotonin activity can indeed be a causal factor in the relapse of clinical depression (Smith, Fairburn, & Cowen, 1997).

There are different ways of responding to this observation. One can say, for example, (a) it is not true; (b) even if it is true, it does not matter; and (c) it is an observation worth trying to understand and integrate into theoretical models. The recent serotonin debate which, to our regret, discomfited Professor Rose revolved around this issue (as well as the reporting and philosophical underpinnings of the scientific method).

Professor Rose makes passing reference to the fact that 'dopamine anomalies were allocated to "schizophrenia"'. The fascination of this heuristic hypothesis was that, in a critical respect, it turned out to be true. There is reliable evidence that acute psychosis, with its protean manifestations, is strongly associated with increased synthesis and release of striatal dopamine (Jauhar, Johnstone, & McKenna, 2022). Antipsychotic drugs attenuate the symptoms of acute psychosis, not by reversing the primary dopamine abnormality (Jauhar et al., 2019; Sigvard et al., 2022), but by blocking the effects of excessive synaptic dopamine at postsynaptic dopamine receptors (Kapur, Zipursky, Jones, Remington, & Houle, 2000). This knowledge, co-produced by researchers and people with schizophrenia, was an important achievement which merits recognition. Such findings facilitate the investigation of underlying mechanisms and hopefully lead to improvements in treatment.

Psychiatric conditions are characterized by disorders in self-consciousness. We agree with Professor Rose that understanding of the neural mechanisms involved in this aspect of mental life is particularly limited. With such a poor knowledge base, how is it that we have any useful pharmacological treatments at all? The answer given by historians of psychopharmacology is 'serendipity' or more accurately, astute observations by patients and clinicians (Healy, 1997). It turned out subsequently that many of these therapeutically helpful agents acted pharmacologically on neurotransmitters and their receptors. In some people with severe clinical depression, simple manipulation of monoamine neurotransmitters can lead to resolution of this complex experiential, psychological, and somatic condition (for a personal account, see McGilchrist, 2017). We find this a remarkable phenomenon, and not one to be massaged into triviality.

Such beneficial effects of antidepressants do not occur as often as they should and both psychological and pharmacological treatments need radical improvement. However, current 'new' pharmacological treatments for depression, for example, ketamine and psilocybin, remain obdurately neurotransmitter-based (Jelen & Stone, 2021; Ling et al., 2022). At first, psilocybin (a drug acting through serotonin receptors) was presented as an agent whose function was to assist psychotherapy. However, a recent formulation has argued that the psychotherapeutic element might reasonably be limited to safety monitoring (Goodwin, Malievskaia, Fonzo, & Nemeroff, 2023). This is an interesting and important discussion of great relevance to people with refractory depression and might indeed be suitable for the 5E approach endorsed by Professor Rose.

We agree with Professor Rose that developments in neuroscience at genetic, cellular, and systems levels are exciting and raise great possibilities for integration with psychological and social approaches as well as improvements in pharmacological and brain stimulatory

treatments. In the meantime, those stubbornly pursuing the fascinating role of serotonin in neuropsychological function and subjective mental experience might take solace from Einstein's comment, 'It's not that I'm so smart, it's just that I stay with problems longer'.

Competing interests. SJ has given educational talks on antipsychotics for Lundbeck, Sunovian, and Jannsen, and a talk on causes of psychosis for Boehringer-Engelheim. He was on a Welcome Panel for Back Translation in Psychiatry, and advised on antipsychotic medication for LB Pharmaceuticals Inc.

References

Goodwin, G. M., Malievskaia, E., Fonzo, G. A., & Nemeroff, C. B. (2023). Must psilocybin always 'assist psychotherapy?' *American Journal of Psychiatry*. https://doi.org/10.1176/appi.ajp.20221043

Healy, D. (1997). *The antidepressant era*. Cambridge, MA: Harvard University Press.

Jauhar, S., Johnstone, M., & McKenna, P. J. (2022). Schizophrenia. *Lancet* (*London, England*), *399*(10323), 473–486. https://doi.org/10.1016/S0140-6736(21)01730-X

Jauhar, S., Veronese, M., Nour, M. M., Rogdaki, M., Hathway, P., Natesan, S., … Howes, O. D. (2019). The effects of antipsychotic treatment on presynaptic dopamine synthesis capacity in first-episode psychosis: A positron emission tomography study. *Biological Psychiatry*, *85*(1), 79–87. https://doi.org/10.1016/j.biopsych.2018.07.003

Jelen, L. A., & Stone, J. M. (2021). Ketamine for depression. *International Review of Psychiatry*, *33*(3), 207–228. https://doi.org/10.1080/09540261.2020.1854194

Kapur, S., Zipursky, R., Jones, C., Remington, G., & Houle, S. (2000). Relationship between dopamine D2 occupancy, clinical response, and side effects: A double-blind PET study of first-episode schizophrenia. *American Journal of Psychiatry*, *157*(4), 514–520. https://doi.org/10.1176/appi.ajp.157.4.514

Ling, S., Ceban, F., Lui, L. M. W., Lee, Y., Teopiz, K. M., Rodrigues, N. B., … McIntyre, R. S. (2022). Molecular mechanisms of psilocybin and implications for the treatment of depression. *CNS Drugs*, *36*(1), 17–30. https://doi.org/10.1007/s40263-021-00877-y

McGilchrist, I. (2017). Depression is not like anything on earth. In C. Foster, & J. Herring (Eds.), *Depression: law and ethics*. Oxford: Oxford University Press.

Sigvard, A. K., Nielsen, M. Ø., Gjedde, A., Bojesen, K. B., Fugløa, D., Tangmose, K., … Glenthøj, B. Y. (2022). Dopaminergic activity in antipsychotic-naïve patients assessed with positron emission tomography before and after partial dopamine D2 receptor agonist treatment: Association with psychotic symptoms and treatment response. *Biological Psychiatry*, *91*(2), 236–245. https://doi.org/10.1016/j.biopsych.2021.08.023

Smith, K. A., Fairburn, C. G., & Cowen, P. J. (1997). Relapse of depression after rapid depletion of tryptophan. *Lancet* (*London, England*), *349*(9056), 915–919. https://doi.org/10.1016/s0140-6736(96)07044-4

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