**Commentary: Recent disputes on the role of serotonin in depression**

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The Commentary is 2235 words long, including references

I have been alternately mystified and exasperated by the recent bad-tempered debate on the role of serotonin in depression in scientific journals (Moncrieff et al, 2022; Juahar et al, 2023) which has been carried into printed and social media. Let me set out some of the key things that seem to me to have been overlooked or sidestepped in this debate.

What we call 'depression' is certainly not one thing, but covers multiple states of being. The word itself has 'looping effects' (Hacking, 1995) in that it brings together these multiple states into an apparent coherence, and pulls in states – feeling sad, loss of motivation, lack of pleasure, etc etc - that might previously or elsewhere have been described, and experienced differently. There is no reason to believe that these different states, or persons feeling in these different states, form a unity in other way – in causes, reasons, array of moods and thoughts, let alone in brain or bodily states.

The psychiatric assessment of depression, as measured by various scales, or by aggregating symptoms as in diagnostic manuals, and used in research, for example in recruitment of cases in to clinical trials, encapsulates that heterogeneity in the range of items included. Thus in the HAM-D, a clinician rates a person's mood, the presence of guilt, of insomnia, of weight loss, of insight with numbers attached and a cut-off score to indicate depression – the same score can be obtained by many different combinations of scores on individual items. In the DSM, as Goldberg pointed out, "a patient who has psychomotor retardation, hypersomnia and gaining weight is scored as having identical symptoms as another who is agitated, sleeping badly and has weight loss ... to declare that all those satisfying the DSM criteria for the diagnosis of major depression are suffering from the same disorder seems like magical thinking" (Goldberg, 2011, p. 226). The illusion of the additivity of ratings and the equivalence of numbers conflates them into a single 'diagnosis'. But there is no reason to assume that a psychiatric diagnosis of depression individuates a single bodily or neurobiological state and every reason to think that the range of states that are so conflated are highly heterogeneous.

The suggestion that each psychiatric diagnosis might be related to an anomaly in a single neurotransmitter system – too much or too little of a neurotransmitter in particular synaptic clefts - dates back to the 1960s and was initially merely an heuristic device (Schildkraut, 1965), which was followed by the allocation of different biogenic amines – catecholamines and indolamines – to particular diagnoses - dopamine anomalies were allocated to 'schizophrenia', serotonin to depression etc. Of course this was understood, at the beginning, to be a heuristic oversimplification, and at that time it was usually believed there were around seven key neurotransmitters - dopamine, adrenaline, serotonin, oxytocin, acetylcholine, glutamate, GABA (γ-aminobutyric acid). However there are now thought to be dozens if not more substances that play a role in the transmission and regulation of neural circuitry in the mammalian brain; at least 60 are now thought to play active roles in brain processes, working in complex ways with one another in neural signalling. Thus the allocation of one transmitter to one function and one

diagnosis and, later, to one (or even two) treatment target(s), seems doubly problematic given heterogeneity of diagnostic categories and heterogeneity of multiple neurotransmitter action and interaction.

Serotonin receptors are not only expressed in brain, but also are involved in multiple other physiological functions including "eating, reward, thermoregulation, cardiovascular regulation, locomotion, pain, reproduction, sleepwake cycle, memory, cognition, aggressiveness, responses to stressors, emotion, and mood" (Charnay & Léger, 2022). There are at least 15 subtypes of serotonin receptors, usually grouped into three major families. In vivo, in relation to all these functions, regulation of serotonin production and uptake is highly variable over minutes, hours and days, and affected by multiple other 'inputs' to the organism and its physiological systems, including diet, exercise, stress etc, and , and regulation of the production and decay of serotonin receptors, is intertwined with multiple other neurotransmitter systems – the one most often mentioned is the norepinephrinergic system, but the complexity of interactions and their temporality is not well understood.

All the above makes clear that while there may be relations between some of the array of states of being we term 'depression' and variations in different aspects of serotonin systems in brain, these will only ever be a small part of the story, with as yet unclear significance (e.g. Jesulola, Micalos, & Baguley, 2018). Thus we not only have studies and hypotheses of the role of norepinephrine in depression (e.g. Maletic, Eramo, Gwin, Offord, & Duffy, 2017), of the crucial role of glutamate in depression, perhaps in part related to the microbiome and the gut-brain axis (Moriguchi et al., 2019), and of the role of dopamine in depression (e.g. Belujon & Grace, 2017) and no doubt many others, each of which is linked to arguments about the role of the neurotransmitters in modulating other neurotransmitters and in modulating neural circuitry in various brain regions hypothetically linked to different elements in the capacious diagnosis of depression .

A broad view of these issues tells us that we certainly don't know enough to attribute a causal role, let alone a major causal role, in any of the states we call depression to a prior, necessary, determinant variation in some aspect of serotonin metabolism or serotonin circuitry. Simply to say that we find correlations between this or that aspect of 'depression' and some variation in some aspect of serotonin metabolism – which may be cause or effect or some combination of the two is to tell us precisely nothing of use, in explanation or in action. Even less so if it is taken in isolation from any understanding of the more general role of the serotoninergic system in neural circuitry and relation with other neurotransmitters and modulators of neural activity -

Further, we need to understand that the brain is not a homeostatic system but is homeodynamic. Hence the key to understanding the neurobiological processes involved in depression and the effects of various types of pharmaceuticals lies in understanding neuroplasticity. For example a temporary increase in one aspect of the neurotransmitter system, such as an increase or decrease in

the availability of certain neurochemicals at some sites in neural circuits, will lead to a consequential upregulation or downregulation of other neuronal receptors (Carlson, Singh, Zarate Jr, Drevets, & Manji, 2006; Liu, Liu, Wang, Zhang, & Li, 2017). In such highly networked and interactive dynamic system, we know little about the implications of artificially changing levels of neurotransmitters by administration of drugs beyond a very few short term and local changes: we do not know the extent to which they spark a cascade of further changes designed to return the system to its previous state, nor do we know, neurobiologically, the consequences of long term chronic administration of these pharmaceuticals, although we are beginning to distinguish the symptomatology of discontinuation from that of relapse ( Murray et al, 2016; Massabki and Abi-Jaoude, 2021).

Given the role of serotonin, like other neurotransmitters, in so many physiological functions, it is obviously the case that disruptions caused by the administration of drugs designed to modulate aspects of the serotonergic system will have wide ranging consequences across the body. The partitioning of these – so that some are to be considered 'effects' and others are 'side effects' or 'adverse effects' depends on the perspective of the maker of those distinctions – eg researcher, clinician, pharmacist, drug company or patient.

What we call depression involves thoughts, feelings, motivations, experiences, beliefs about oneself and others and much more – to that extent it is not merely embrained but embodied, extended or emplaced (located in a particular time and place), enacted (not just a matter of experience but of a way of being and acting), embedded in a particular niche or way of being, and encultured (shaped by the linguistic resources and belief systems of particular cultures). This is what one might term a 5E approach to mental health.

Thus, to state the blindingly obvious, there is much more to neural activity, and variations of neural activity, in the (human) brain than neurotransmitters! If we think, as is now common, of neural circuitry –a metaphor employed extensively in popular debates about neurodiversity ("my brain is wired differently") - we know very little about the complexity of neural circuitry involved in any 'mental' process that we describe in normal language, whether that be cognition, memory, belief, emotion, feeling, intention, agency etc., let alone the problematic issues of consciousness, or in general the 'emergence' of what are sometimes termed 'higher mental functions' from the 'mere meat' of the brain.

We do know that there is rapid turnover of neurons in the brain, not only during periods of rapid synaptic pruning and synaptic remodelling in early childhood and at puberty but throughout life, with neurogenesis now plausibly, though disputedly, believed to occur into adulthood in humans and to be highly responsive to 'exposures' such as diet, stress, some pharmaceuticals, practical learning, exercise and other bodily exposures. To use the popular expression, there is much evidence that the human brain is capably of 'rewiring itself' in relation to such exposures and

indeed, to the extent that humans are able to create new memories, learn new skills, and undertake novel activities until old age gives credence to the neuroscience of neuroplasticity.

Our growing knowledge of epigenetics suggests the pathways through which these exposures can achieve these effects. One key pathway is via the regulation of gene expression in the brain. As somewhere over 75% of the genetic sequences in the human are expressed in brain tissue, modulation of the expression of some or all of these genetic sequences as a result of certain exposures gives credence to an emphasis on the importance of the 'plasticity' of each and all of the elements of neural circuitry in relation to factors affecting gene activation and deactivation, popular examples being via the stress reactions, via the microbiome or via inflammation. These are among the key neurobiological issues currently being studies in 5E approaches to mental distress.

In short, given the above, one cannot help but feel that the whole way in which the current debate on the role of serotonin in depression and the efficacy or otherwise of pharmaceuticals designed to act on the serotonin system, has a remarkably naïve and blinkered view of the brain, neurotransmitters, neural circuits, not to mention the embodied, o emplaced, and encultured character of those states we have come to call depression.

I have no financial interests to declare, and the work that led to this commentary was not financially supported by any institution or grant awarding body.

## References


Belujon, P., & Grace, A. A. (2017). Dopamine system dysregulation in major depressive disorders. *International Journal of Neuropsychopharmacology, 20*(12), 1036-1046.

Carlson, P. J., Singh, J. B., Zarate Jr, C. A., Drevets, W. C., & Manji, H. K. (2006). Neural circuitry and neuroplasticity in mood disorders: insights for novel therapeutic targets. *NeuroRx, 3*(1), 22-41.

Charnay, Y., & Léger, L. (2022). Brain serotonergic circuitries. *Dialogues in Clinical Neuroscience*, 12(4), 471-487

Gehred, M. Z., Knodt, A. R., Ambler, A., Bourassa, K. J., Danese, A., Elliott, M. L., . . . Ramrakha, S. (2021). Long-term neural embedding of childhood adversity in a population-representative birth cohort followed for 5 decades. *Biological Psychiatry, 90*(3), 182-193.

Goldberg, D. (2011). The heterogeneity of "major depression". *World Psychiatry, 10*(3), 226-228.

Hacking, I. (1995). The looping effects of human kinds. In D. Sperber, D. Premack, & A. J. Premack (Eds.), *Causal cognition: a multi-disciplinary approach* (pp. 351-383). Oxford: Clarendon Press.

Jauhar, S., Arnone, D., Baldwin, D. S., Bloomfield, M., Browning, M., Cleare, A. J., . . . Fu, C. (2023). A leaky umbrella has little value: evidence clearly indicates the serotonin system is implicated in depression. *Molecular Psychiatry*, 2023, 1-4.

Jesulola, E., Micalos, P., & Baguley, I. J. (2018). Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model-are we there yet? *Behavioural Brain Research, 341*, 79-90.

Liu, B., Liu, J., Wang, M., Zhang, Y., & Li, L. (2017). From serotonin to neuroplasticity: evolvement of theories for major depressive disorder. *Frontiers in Cellular Neuroscience,* 11, 305.

Maletic, V., Eramo, A., Gwin, K., Offord, S. J., & Duffy, R. A. (2017). The role of norepinephrine and its α-adrenergic receptors in the pathophysiology and treatment of major depressive disorder and schizophrenia: a systematic review. *Frontiers in Psychiatry, 8*, 42.

Massabki, I., & Abi-Jaoude, E. (2021). Selective serotonin reuptake inhibitor 'discontinuation syndrome' or withdrawal. *The British Journal of Psychiatry, 218*(3), 168-171. doi:10.1192/bjp.2019.269

Moncrieff, J., Cooper, R. E., Stockmann, T., Amendola, S., Hengartner, M. P., & Horowitz, M. A. (2022). The serotonin theory of depression: a systematic umbrella review of the evidence. *Molecular psychiatry*, 2022, 1-14.

Moriguchi, S., Takamiya, A., Noda, Y., Horita, N., Wada, M., Tsugawa, S., . . . ElSalhy, M. (2019). Glutamatergic neurometabolite levels in major depressive disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies. *Molecular Psychiatry, 24*(7), 952-964.

Murray, R. M., Quattrone, D., Natesan, S., van Os, J., Nordentoft, M., Howes, O., . . . Taylor, D. (2016). Should psychiatrists be more cautious about the long-term prophylactic use of antipsychotics? *The British Journal of Psychiatry, 209*(5), 361-365.

Schildkraut, J. J. (1965). The catecholamine hypothesis of affective disorders: A review of supporting evidence. *American Journal of psychiatry, 122*, 509-522.