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Conference paper

Brief review

THE MYTH OF SEROTONIN THEORY OF DEPRESSION: AN ANALYSIS OF UMBRELLA REVIEW METHODOLOGIES AND CLINICAL IMPLICATIONS

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SUMMARY

The serotonin theory of depression, long a dominant paradigm in psychiatry, has been recently challenged by a comprehensive umbrella review by, which concludes that there is no consistent evidence linking serotonin activity to depressive disorders. This article critically analyzes that review alongside two major commentaries that raise substantial methodological and interpretative concerns. Focusing on review design, inclusion criteria, quality assessment tools, and neuropharmacological interpretations, we highlight the extent to which methodological limitations can shape the conclusions of evidence syntheses. While Moncrieff's work provokes valuable scientific debate, its post-hoc protocol amendments, selective reporting, and down-weighting of serotonergic findings weaken its conclusiveness. We argue for a more nuanced understanding of serotonin's role in depression, not as a sole cause but as a potential modulatory factor in vulnerable populations. The implications for clinical practice and public communication are discussed.

Key words: *serotonin theory – depression - umbrella review*

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INTRODUCTION

The serotonin hypothesis of depression emerged in the 1960s and became widely influential in the 1990s with the commercial success of selective serotonin reuptake inhibitors (SSRIs) (Moncrieff et al. 2022). It posited that depression stems from low serotonin levels or function in the brain, a view that has shaped both research agendas and public understanding. Despite increasing skepticism in the scientific community, the theory remains prominent in medical texts and mental health communication (Jauhar et al. 2023). Moncrieff et al. (2022) attempted to settle the debate through an umbrella review which concluded that the theory lacks empirical support. However, the study has generated intense criticism regarding its methodology and interpretation of data. In this article, we analyze the strengths and weaknesses of the umbrella review and contrast its claims with those of two major critiques by Jauhar et al. (2023) and Smith et al. (2024), evaluating their implications for clinical psychiatry.

SUBJECT AND METHODS

We conducted a narrative critical analysis of three peer-reviewed articles: the umbrella review by Moncrieff et al. and two responses. The selection was based on their centrality to the current debate on serotonin and depression. We analyzed the methods of study inclusion, the application and modification of appraisal tools (GRADE and AMSTAR-2), and the scientific validity of conclusions drawn from molecular imaging and tryptophan depletion data (Smith et al. 2024). The analysis included evaluating whether methodological frameworks were transparently applied and consistent with umbrella review standards (Fusar-Poli & Radua 2018).

THE INFLUENCE OF ENVIRONMENTAL FACTORS

The controversy illustrates the tension between reductionist biological models and critical psychiatry. While Moncrieff et al. (2022) contribute to dismantling the oversimplified "chemical imbalance" narrative, their review suffers from methodological inconsistencies that undermine its authority. Notably, several high-quality studies show serotonergic alterations in specific populations (e.g., those with a family history of depression or after SSRI treatment withdrawal), suggesting that serotonin may not be irrelevant but context-dependent (Ogawa et al. 2014; Yeh et al. 2015).

A rigid dismissal of serotonin's role risks ignoring the complexity of neurobiological modulation and therapeutic response. As Jauhar et al. (2023) argue, reductions in SERT or 5-HT1A binding observed in molecular imaging may reflect true pathophysiological differences rather than artifacts of prior antidepressant use (Gryglewski et al. 2014; Meyer 2007). The same applies to tryptophan depletion, where negative findings in healthy controls do not invalidate positive findings in clinical samples (Pu et al. 2021).

A compelling analogue to this complexity can be found in addiction studies. Bruce K. Alexander's "Rat Park" experiment in the late 1970s showed that rats housed in enriched, socially stimulating environments consumed significantly less morphine solution than those isolated in standard laboratory cages. The findings suggested that drug use was less about pharmacological inevitability and more about the interaction between substance and environment. When the environment allowed for socialization, play, and exploration, the desire for artificial reward was significantly diminished (Alexander et al. 1981).

Similar reflections can be made in the context of depression. Recent integrative reviews on the biological, psychological, and social determinants of depression emphasize that adverse social environments - including isolation, lack of social support, and poor living conditions - can significantly elevate the risk of depressive disorders. Conversely, enriching the environment through supportive relationships and community cohesion shows protective effects (Scandolara et al. 2022). Longitudinal studies, such as those conducted with the Northern Finland Birth Cohort, have found that early social adversity like bullying or emotional neglect is predictive of adult depression, while positive family interactions act as strong protective factors (Kiviruusu et al. 2020).

These findings support a biopsychosocial model where environmental and relational factors are not secondary to neurobiology but integral to the etiology and course of depression. Just as the Rat Park experiment reframed our understanding of addiction, current evidence urges a similar reframing of depression - not as a fixed neurochemical deficit but as a dynamic interaction between brain, experience, and social world.

CONCLUSIONS

Moncrieff's umbrella review raises critical questions about the evidentiary base of the serotonin theory but fails to meet the methodological rigor required to dismiss it conclusively. Serotonin should not be viewed as a direct cause of depression, but neither can its modulatory role be excluded. Clinicians and researchers should avoid deterministic messaging and acknowledge the multifactorial nature of depression, including genetic, environmental, and neurochemical dimensions.

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