


Letter to the Editor

The use of psychedelics in psychiatric treatment – evolutionary perspectives

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The past two decades have seen renewed interest in psychedelics such as psilocybin and other novel approaches such as MDMA (3,4-Methylenedioxymethamphetamine) and ketamine in the treatment of depression and other psychiatric disorders. This interest is partly driven by disappointment with the efficacy and side effects of standard drugs and partly by an attraction to the mystique of ‘natural’ methods. However, it has been pointed out that the psychedelic research base is potentially flawed due to factors such as participant self-selection and expectancy, difficulties with blinding and ideological motives as conflicts of interest driving researchers to inflate the importance of findings (Ritchie, 2022).

Although research to date is promising, it has been rare to find a nuanced and dispassionate discussion with recent exceptions (Madras, 2022; Naudet *et al.* 2022). General media reporting can then further raise expectations and even lead to calls for public health policy changes. These involve loosening governmental restrictions on use of psychedelics without sufficient evidence of their safety. Ultimately, this may lead to false expectations among patients and potential exposure to significant adverse effects associated with use of such agents, analogous to the association of psychosis and deregulation of cannabis in specific populations.

Clinicians and researchers are therefore urged to temper expectations and to deflate the ‘psychedelic hype bubble’, thus leading the way to more rigorous scientific scrutiny of the benefits and adverse effects of psychedelics in psychiatric treatment (Yaden *et al.* 2022). Just as extreme affective shifts can be stabilised through psychotropic medication, can evolutionary psychiatry stabilise the extreme narrative shifts to gently deflate this bubble? It may be the case; psychedelic and associated therapy is yet another treatment modality in the toolkit of psychiatrists managing psychiatric disorders. Promisingly, the largest and most rigorous trial to date reported psilocybin at a single dose of 25 mg reduced depression scores significantly more than a 1 mg dose over the same period (Goodwin *et al.* 2022). Rigorous trials such as these may allow for ‘deflating of the bubble’ so that clear efficacy and tolerability of psychedelics may be determined.

Evolutionary psychiatry extends the currently limited interpretation of the biopsychosocial model and raises fundamental and novel questions about mental health, mental illness and treatments. The evolutionary perspective focuses on both ultimate (why) and proximate (how) questions in relation to mental illness and its treatment.

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For example, the evolutionary perspective acknowledges the potential benefits of low mood in the context of, for example, loss, the potential benefits of mildly elevated mood in propitious situations and the fact that these normal ‘moodostat’ mechanisms may be what go awry in mood disorders, whereby pathological mood changes lead to considerable distress and dysfunction. Examples of questions posed by an evolutionary perspective may be: ‘why do these psychedelics have any benefit at all, and how does that change our understanding of mental disorders?’ (ultimate), and ‘how can we identify patient groups that would most benefit from psychedelics and simultaneously be at the lowest risk of harm?’. Additionally, it may be the case that there is more to glean from the experience than the ‘simple’ biopsychosocial model. For example, it may be conceivable that a particular psychedelic alone may be less therapeutic than when accompanied by the assisted psychotherapy, ritual and setting.

Regarding the use of psychedelics and other novel psychotropic agents, the evolutionary perspective begins by asking which biological systems are useful potential treatment targets or ‘substrates’. For example, the bipartite model of serotonergic functioning focusing on the effects of post-synaptic 5-HT_{1A}R and 5-HT_{2A}R signalling describe how selective serotonin reuptake inhibitors (SSRIs) and psychedelics mediate emotional modulation or release, both leading to a reduction in depressive symptoms. A key question posed by researchers is whether chronic SSRI use obstructs the potential therapeutic action of psilocybin, producing divisive opinions on whether the target population are to be treatment-resistant or treatment-naïve (Carhart-Harris & Goodwin, 2017). An evolutionary lens can determine why depression arises in particular patients, the nature of their depressive symptoms and potentially which patient populations may benefit most from psychedelic-assisted therapy. Additionally, it can provide clarity and richness in explaining differences in participants and experiences. The evolutionary perspective also asks broader questions about the use of psychedelics in our phylogenetic past, in modern hunter-gatherer societies and even among other primates. For example, the ‘Stoned Ape Theory’ developed by Terence and Dennis McKenna purports consciousness has roots in psilocybin (McKenna, 1993). Furthermore, the use of psychedelics in ancient and recent history is strongly linked to shamanism, and authors have called for integrating traditional shamanic models to optimally assess clinical efficacy and safety (Bravo & Grob, 2012). Moreover, the setting and ritual frameworks provided by shamanic biogenetic paradigms surrounding psychedelic-assisted therapy appear to play a key role in efficacy and tolerability (Winkelman, 2021).

Psychedelic states are known to produce heightened sensitivity to the environment (Carhart-Harris *et al.* 2015; Kaelen *et al.* 2015;

Hartogsohn, 2016). Therefore, questions relating to the cultural and societal salience of psychedelic drug use are also raised by the evolutionary perspective, such as the use of psychedelics in religious and 'shamanic' practices and their potential role in group rituals in enhancing group cohesion and bonding (Dunbar, 2022). To this effect, recent studies have begun to demonstrate the effect of psychedelic-assisted group therapy for demoralisation and attachment insecurity in those with serious medical illnesses (Anderson *et al.* 2020; Stauffer *et al.* 2020). Additionally, a pilot study has explored nature relatedness and ayahuasca retreats which has shown to correlate positively with mindfulness and, negatively with depression and anxiety (Ruffel *et al.* 2022). Further research may elucidate the relative contributions of each of these 'multidimensional interventions' (psychedelic, ceremony/ritual and setting).

An evolutionary approach here may allow us to look past the rigid paradigm of conventional psychotropic research, predominantly based on idealistic randomised controlled trials. Instead, we may develop a rigorous multi-faceted model of research also placing emphasis on for example, well-designed naturalistic and observational studies. This may allow for capturing of novel evolutionary insights into the role of psychedelics in psychiatry. Evolutionary perspectives also allow for broader and more pragmatic measures of health and illness, placing the individual in their wider social context. A notable example being the SOCIAL acronym (social situation, occupation, children and family, income, abilities, love, and sex) developed by Randolph Nesse, which can be used to guide a broader definition of health and wellbeing (Nesse, 2019), allowing psychiatry to pivot away from measuring outcomes as mere reductions on questionnaires. Furthermore, as research on psychedelics has largely used subjective measures, rigour may be achieved through placing greater emphasis on objective measures, particularly those that align with evolutionary perspectives. These may include levels of interpersonal functioning, fitness and reproductive success, geo-location (simple motor activity) (Palmius *et al.* 2017), and regulation of sleep through digital trackers (Aledavood *et al.* 2019).

These additional biological and sociocultural questions, informed by an evolutionary perspective, are likely to help bring much-needed scientific rigour to evaluating psychedelic use in psychiatry. This perspective may allow novel insights into the recruitment of subjects, individual and population benefits, and adverse effects of therapy and provide caution in our understanding of the implications of a narrow view of psychedelics in research via cultural evolution theory. Furthermore, these evolutionary perspectives can be generalised to the study of other novel and existing psychotropic agents in psychiatry (Abed & St John-Smith, 2022).

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