

less highlights the need for more effective medication options to manage depressive episodes in people with bipolar disorder.

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Modulating self-referential processing through meditation and psychedelics: is scientific investigation of self-transcendence clinically relevant?

Self-referential processing is a core feature of human experience and includes a variety of mental faculties that support conception of the self, including internal representations that associate salient information to one's identity. It is well understood that self-referential processing is important for the onset, maintenance, prevention and treatment of psychiatric conditions, including mood, anxiety and substance use disorders. Here we propose that meditation and psychedelics may modulate self-referential processing by inducing self-transcendence, and call for further research on this transdiagnostic mechanism of action.

Meditation and psychedelics have gained renewed traction in psychiatry after initial interest in the 1970s. Meditation is a form of cognitive training with the goal of improving attentional and emotional self-regulation and inducing self-transcendence. Psychedelics are powerful psychoactive substances that alter perception and mood; affect numerous cognitive processes, including the sense of self; and have been preliminarily shown to have therapeutic effects in mood and anxiety disorders.

It can be argued that meditation science has undergone two epochs, and that we are currently entering a third. The first epoch, which occurred approximately between 1995 and 2005, was characterized by two types of studies. The first set of studies provided initial, and then replicated, results indicating therapeutic effects of meditation across many domains (e.g., depression, anxiety and pain), with variable effect sizes. A concurrent second set of studies provided initial investigation of differences between experienced meditators and novices, focusing on heretofore unexplored effects of meditation on the brain. The second epoch, roughly 2005-2020, was characterized by increasingly rigorous, full-scale randomized controlled trials (RCTs) and mechanistic research to elucidate cognitive-affective mechanisms that might underlie meditation's health-related benefits. For example, researchers used functional neuroimaging to investigate attention and emotion regulation, and the relations of these processes to health and well-being, including psychiatric outcomes.

We suggest that meditation research is entering now a third phase, moving beyond the focus on its attention and emotion reg-

ulatory mechanisms, and toward the study of advanced meditation, that is, states and stages of practice that unfold with increasing mastery, including more profound psychological transformations, such as self-transcendence and non-dual awareness (i.e., the experiential unification of the subject-object dichotomy that normally structures human experience). The clinical outcomes and neural mechanisms of such self-transcendent experiences have now begun to be studied in the context of psychedelic-assisted psychotherapy.

To date, the effect of meditation has been predominantly explored through a lens of stress reduction. For example, mindfulness-based stress reduction, the best known and most widely applied manualized intervention based on meditation, was designed to reduce participants' stress, although it was later found to be effective also in reducing anxiety and depression symptom severity in a broad range of individuals. We are now on the cusp of a new wave of research and clinical applications that instead focus on aspects of advanced meditation, including self-transcendence.

Self-transcendence – characterized by ego dissolution, affective bliss, and a merging or softening of boundary between self and other/object (i.e., non-duality) – is a phenomenological experience reported across multiple contemplative, philosophical, religious and spiritual traditions around the world for thousands of years. This experience is valued as a catalyst for compassionate behavior and self-actualization. Considerable evidence indicates that psychedelics can induce radical experiences of self-transcendence. We argue that self-transcendence, and what have been called altered states of consciousness or peak experiences, should be a legitimate area of study. We believe that it is now warranted to rigorously interrogate these phenomena in the context of modern psychiatry, and that this pursuit may provide new avenues to foster psychological thriving in clinical and non-clinical contexts.

In a RCT (N=165), we recently found that a mindfulness-based intervention for opioid misuse elicited self-transcendent experiences marked by ego dissolution, bliss, and non-dual awareness to a significantly greater extent than an active psychotherapy control¹. Self-transcendent experiences were associated with increased

frontal midline theta EEG power during meditation, which mediated effects of mindfulness-based intervention on decreasing opioid misuse through a 9-month follow-up. These effects were robustly replicated in another study². Two other recent RCTs have shown that developing increased self-transcendence through meditation is associated with decreases in chronic pain^{3,4}.

Psychedelics have also been linked to self-transcendence in clinical trials⁵, and some neuroimaging studies have identified associations between self-transcendence (sometimes called ego-dissolution in the psychedelic literature) and deactivation of the default mode network⁶ and activation of cortico-striato-thalamo-cortical circuitry⁷.

The study of self-transcendence, and other aspects of advanced meditation, will benefit from a more nuanced understanding and testing of the phenomenology of these experiences, the kinds of practices that lead to them, and their developmental trajectories (meditative development) and outcomes (meditative endpoints). Neuroimaging studies of self-transcendence and advanced meditation more broadly (e.g., related to altered perception of time, space and reward-related processes) could provide mechanistic understanding to inform computational models of modulating aberrant neural systems (e.g., dysfunctional self-referential processes implicated in psychiatric disorders and modulated by meditation and psychedelics⁸).

Ultimately, this line of research has the potential to stimulate the development of novel treatments for psychiatric illness, including combination therapies that integrate existing mindfulness-based interventions and psychedelics, novel meditation-based therapies grounded in contemplative traditions and practices not yet extensively studied by Western science⁹, and novel neuromodulation protocols to target neural networks with neurofeedback and brain

stimulation.

Self-transcendent experiences may prove to be a means of restructuring the neural system dysfunction that underlines the development and maintenance of a range of maladaptive behaviors and mental states. By pursuing this scientific frontier to deeply understand advanced meditation, including meditative development and endpoints, and psychedelic-assisted psychotherapy, we may access a great and untapped potential to alleviate suffering and advance human flourishing.

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Clinical translation of expert-endorsed cognitive rehabilitation interventions for substance use disorders

In a recent Delphi consensus¹, we endorsed the application of four cognitive rehabilitation interventions as adjuncts to the treatment of substance use disorders: cognitive bias modification, contingency management, cognitive remediation, and emotion regulation training. This innovative portfolio is poised to cover the unaddressed need of tackling cognitive alterations that can hinder the efficacy of current treatments for substance use disorders². Here, we summarize the therapeutic mechanisms of these four interventions, discuss barriers to their translation into clinical practice, and provide recommendations on how to overcome these barriers.

Cognitive bias modification is a family of interventions that aim to reset drug-related biases using different varieties of computerized cognitive training. One example redirects tendencies to approach the drug toward alternative targets (e.g., from a tendency to approach alcohol to a tendency to approach a non-alcoholic drink). Contingency management provides tangible incentives (e.g., monetary payments) in exchange for therapeutic goal achievement (e.g.,

treatment attendance, abstaining or reducing drug use). Both cognitive bias modification and contingency management target addiction-related alterations in the incentive salience system by reducing the value of drug rewards and increasing the value of alternative reinforcers³.

Cognitive remediation trains mental strategies aimed to restore or circumvent cognitive deficits, with a view to improving everyday function. For example, a “pause – check your goal – choose” strategy can be used to thwart impulsive choices within high-risk scenarios such as social engagements (especially those involving people who use drugs) or family gatherings, which can be highly confrontational for people in recovery. Emotion regulation training also uses a variety of mental strategies, in this case focused on improving management of negative emotions (e.g., cognitive reappraisal) and enhancing positive affect (e.g., savouring of natural reinforcers). Both cognitive remediation and emotion regulation interventions target addiction-related alterations in the executive control