Psilocybin increases brain network integration in patients with depression

Clinical trial results show that psilocybin, a potent psychedelic, has antidepressant effects in patients with depression and is more effective than escitalopram. Functional MRI experiments revealed a decrease in brain modularity after psilocybin therapy, indicative of an increase in the global integration of the brain's functional networks.

This is a summary of:
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The mission

Patients with depression struggle with persistent low mood and repetitive negative thoughts[1]. Unfortunately, even the best-performing antidepressants require long-term compliance, are not without side effects and have only modest efficacy[2], which emphasizes the need for new, improved treatments. Pioneering clinical trials have indicated that one or two doses of psilocybin, found in so-called 'magic mushrooms', can have rapid, substantial and sustained antidepressant effects when combined with psychological support, even in patients who are 'treatment resistant'[3]. The antidepressive mechanisms of psilocybin are poorly understood, although recent functional MRI (fMRI) studies (Imperial College London's pioneering fMRI) have revealed robust increases in global brain integration and flexibility after psilocybin ingestion[4]. Tellingly, this pattern starkly contrasts with the abnormally rigid and segregated depressed brain[5]. We sought to assess whether the same increase in global brain integration is evident longer term after psilocybin therapy for depression, which might reflect a 'carryover' of the drug's acute brain effects.

The discovery

We analyzed data from two separate clinical trials of depression. The first was a 1-week trial of orally administered psilocybin, and the second was a double-blind phase 2 randomized controlled trial comparing psilocybin therapy to escitalopram, a conventional antidepressant. In both trials, psilocybin therapy worked rapidly and robustly to decrease depressive symptom severity (Fig. 1a, b). In the second trial, a 64% reduction in depression severity scores was observed 3 weeks after two psilocybin therapy sessions, compared with a 37% reduction at the end of a 6-week course of daily escitalopram, indicative of the superior efficacy of psilocybin therapy over escitalopram (Fig. 1b).

To gain insight into the mechanism of action of psilocybin, we analyzed fMRI scans from both trials. We observed a decrease in brain modularity after psilocybin therapy (Fig. 1c, d), an effect that was strongest for 'higher-order' brain systems and correlated with symptom improvements. These changes in brain function suggest an increase in the global integration of functional networks within the brain and are consistent with psilocybin's breaking open the abnormally rigid patterns of functioning that are often observed in depression[5]. Interestingly, no changes in global brain integration were observed after treatment with escitalopram (Fig. 1e), which suggests that psilocybin acts differently than conventional antidepressant medications do.

Future directions

There is growing evidence for the viability of psychedelic therapy as a treatment option in psychiatry; however, understanding of the underlying mechanisms is still rudimentary. We suspect that disorders characterized by cognitive and behavioral rigidity, such as depression, might be particularly amenable to psychedelic interventions, via a hypothesized action on brain integration. Addressing how psychedelic therapy acts on the brain to treat mental illness is essential and will provide biological understanding of and plausibility for a therapeutic model that remains paradigm challenging, both scientifically and politically.

Phase 3 trials are planned or underway to assess the safety and efficacy of psychedelic therapy at a greater scale. Better understanding of the mechanisms will require more studies testing the robustness and replicability of increased global brain integration after psychedelic therapy. Moreover, it will be important to ascertain whether these brain effects translate across diagnostic categories and mental health spectra, whether they are sustained, whether they are necessary and sufficient for positive responses to psychedelics and whether they are specific to psychedelic therapy or are also observable with other treatments.

Developments in whole-brain, dynamic, network-based analyses will enable the description of human brain function at a level that more naturally maps to lived experience. It is with the benefit of these advances in cognitive neuroscience that we are now able to offer a plausible, empirically guided neurobiological model of the therapeutic action of psychedelics; that is, one that states that psychedelic therapy 'opens up' global brain integration in disorders in which the brain and mind have become 'stuck' in maladaptive patterns of functioning.

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EXPERT OPINION

"This report by Daws and colleagues is an important step forward in our understanding of the network-level mechanisms mediating psilocybin's antidepressant effects." **Conor Liston, Weill Cornell Medicine, New York, NY, USA.**

FIGURE

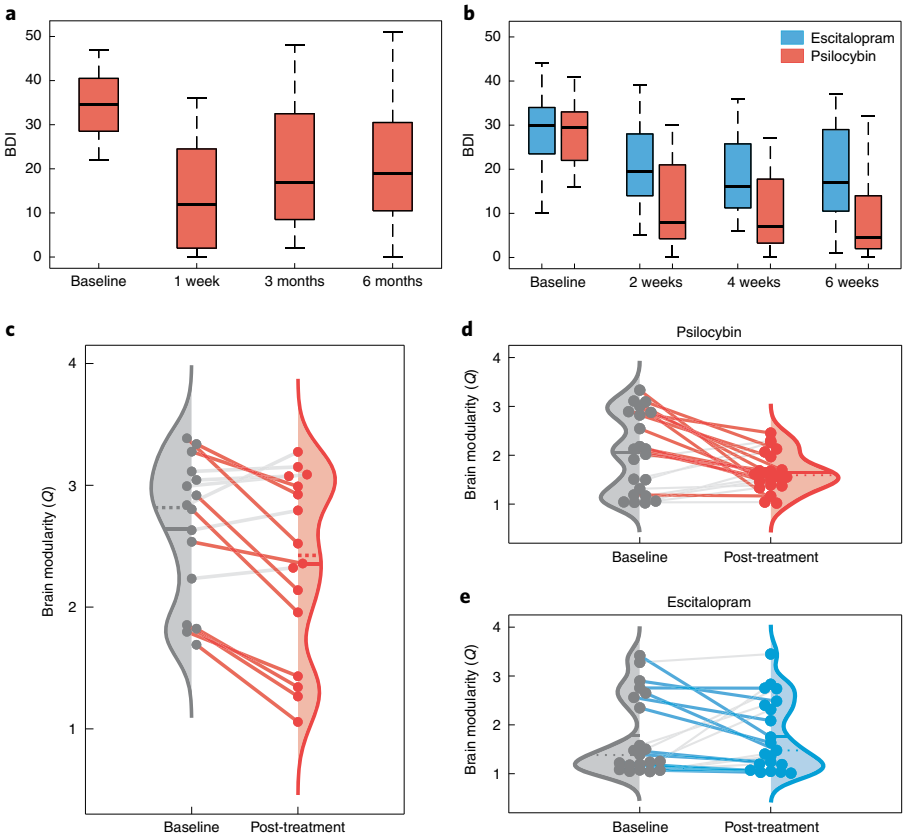

Fig. 1 | Psilocybin's antidepressant effect relates to increases in the global integration of brain functional networks. a, Rapid and sustained reduction in depression severity (as determined by Beck's depression inventory (BDI)) after psilocybin therapy in patients with treatment-resistant depression. **b**, Antidepressant effect similar to that in **a**, observed in patients with major depressive disorder, in which psilocybin was superior to escitalopram. **c,d**, Decreased brain network modularity indicates that psilocybin's antidepressant action relates to a global increase in between-network connectivity in patients with treatment-resistant depression (**c**) or major depressive disorder (**d**). **e**, No action such as that in **c**,**d** was observed in response to escitalopram.

BEHIND THE PAPER

Early, philanthropically funded fMRI research carried out at Imperial College London revealed acute changes in brain function with psilocybin that were suggestive of antidepressant potential. This work inspired the first of two clinical trials designed to assess the safety and efficacy of psilocybin therapy for the treatment of depression. The first was backed by a UK Medical Research Council award, but subsequent work required philanthropic backing, which came via the Alexander Mosley Charitable Trust and founders of the Centre for Psychedelic Research at Imperial College London. Psychedelic medicine is now a billion-dollar industry — a remarkable fact, given that the majority of psychedelics are still illegal to use in most jurisdictions — but much of the early research of this current era has depended on charitable donations and researcher stamina in the face of practical and political challenges. **R.C.-H.**

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FROM THE EDITOR

"This study suggests that the naturally occurring psychedelic psilocybin produces antidepressant effects in patients with treatment-resistant depression in a way that is distinct from that of conventional antidepressants. Instead of dampening brain activities, psilocybin liberates the entrenched depressed brain, making it more integrated and flexible." **Editorial Team, *Nature Medicine*.**