Decreased brain modularity after psilocybin therapy for depression.

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Abstract

Importance Psilocybin therapy shows antidepressant potential; our data link its antidepressant effects to decreased brain network modularity post-treatment.

Objective To assess the sub-acute impact of psilocybin on brain activity in patients with depression.

Design Pre vs post-treatment resting-state functional MRI (fMRI) was recorded in two trials: 1) Open-label treatment-resistant depression (TRD) trial with baseline vs 1 day post-treatment fMRI (April-2015 to April-2016); 2) Two-arm double-blind RCT in major depressive disorder (MDD), fMRI baseline vs 3 week after psilocybin-therapy or 6 weeks of daily escitalopram (January-2019 to March-2020).

Setting Study visits occurred at the NIHR Imperial Clinical Research Facility.

Participants Adult male and female patients with TRD or MDD.

Intervention(s) (for clinical trials) or Exposure(s) (for observational studies)

Study 1: Two oral doses of psilocybin (10mg and 25mg, fixed order, 7 days apart). fMRI was recorded at baseline and one day after the 25mg dose. Study 2: either: 2 x 25mg oral psilocybin, 3 weeks apart, plus 6 weeks of daily placebo ('psilocybin-arm'), or 2 x 1mg oral psilocybin, 3 weeks apart, plus 6 weeks of daily escitalopram [10-20mg] ('escitalopram-arm'). fMRI was recorded at baseline and 3 weeks after the 2nd psilocybin dose, which was the final day of the 6-week daily capsule ingestion.

Main Outcome(s) and Measure(s) Beck Depression Inventory and fMRI network modularity.

Results Study 1: In 16 adults (mean age [SD], 42.8 [10.1] years, 4 [25%] female), psilocybin therapy was associated with markedly decreased BDI scores at 1 week (mean difference, -21; 95% CI=[-27.3, -14.7], $P<.001$) and 6 months (mean difference, -14.19; 95% CI=[-21.3, -7.1], $P<.001$). Decreased network modularity at one day post-treatment correlated with treatment response at 6 months (Pearson, 0.64; $P=.01$). Study 2: In 43 adults (42.7 [10.5] years, 14 [33%] female), antidepressant effects favoured the psilocybin-arm at 2 (mean difference, -8.76; 95% CI=[-13.6, -3.9], $P=.002$) and 6 weeks (mean difference, -8.78; 95% CI=[-15.6, -2.0], $P=.01$). Specific to the psilocybin-arm, improvements at the 6-week primary endpoint correlated with decreased network modularity (Pearson, -0.42, $P=.025$).

Conclusions and Relevance Consistent efficacy-related functional brain changes correlating with robust and reliable antidepressant effects across two studies suggest a candidate antidepressant mechanism for psilocybin therapy: decreased brain network modularity.

Trial registration ClinicalTrials.gov identifier: NCT03429075

Key Points

Question

How does psilocybin therapy affect spontaneous brain activity post-treatment?

Findings

In two independent trials, an open-label (n=16) and a randomised control trial (n=43), improvements in depressive symptom severity were accompanied by decreases in brain modularity that were related to the antidepressant effects of psilocybin.

Meaning

Two independent trials reveal converging evidence for psilocybin's antidepressant action, namely, less modular brain dynamics.

Introduction

Depression is a highly prevalent mental health condition ¹, the incidence of which has increased during the Covid-19 pandemic ², e.g., as reflected in increased prescriptions of antidepressant medications ³. However, even the best performing antidepressant drugs show modest efficacy ⁴, non-negligible side effects ⁵, discontinuation problems ⁶, and high relapse rates ⁷, highlighting the need for new improved treatments ⁸.

Patients with a diagnosis of depression often exhibit a negative cognitive bias, characterised by pessimism ⁹ poor 'cognitive flexibility' ¹⁰, rigid thought patterns ¹¹ and negative fixations regarding oneself and future prospects ⁹. A number of authors have directly or indirectly taken inspiration from dynamical systems theory to describe depressive episodes as 'attractor states', i.e., stereotyped states with 'gravitational pull' ^{12,13}.

Neuroimaging research has consistently found examples of abnormal brain functioning in depression, resonant with its phenomenology ¹⁴⁻¹⁶. A hierarchically supraordinate intrinsic brain network ¹⁷, the default mode network (DMN), is associated with introspection and self-referential thinking ¹⁸ and these functions are often overactive in depression ⁹. Indeed, several studies have linked excessive engagement of DMN functioning with depressive symptomatology ^{19,20}.

In addition to the DMN, other higher-order brain networks such as the executive (EN) and salience networks (SN) have been implicated in depression ²¹⁻²³. These networks are associated with the 'cognitive control' of thoughts and attention switching ^{24,25} between introspective thought and an external focus ²⁶. Such attentional switching is impaired in depression ²⁷. Tellingly, the serotonin 2A (5-HT_{2A}) receptor subtype, which is the key proteomic binding-site of 'classic' serotonergic psychedelic drugs, such as 'psilocybin' ²⁸, is most densely expressed in a broad pattern of cortex that closely resembles a conjunction map of the DMN, EN and SN ²⁹, corresponding to the transmodal portion of the brain's principal hierarchical gradient ¹⁷.

In the last 15 years, at least six separate clinical trials have reported impressive improvements in depressive symptoms with psilocybin therapy ³⁰. Included among these studies are: 1) an open-label trial in treatment-resistant depression ³¹, and 2) a double-blind randomised controlled trial (DB-RCT) with an active comparator, the selective serotonin reuptake inhibitor (SSRI) and conventional antidepressant, escitalopram ³². These two trials, which included pre and post-treatment functional magnetic resonance imaging (fMRI), are the focus of the present paper's analyses.

The therapeutic action of psilocybin and related psychedelics is incompletely understood. However, one model proposes that psychedelics cause a 5-HT_{2A} receptor induced dysregulation of spontaneous population-level neuronal activity, linked to a temporary 'disintegration' of intrinsic functional brain networks ³³ and a hypothesised decrease in the precision-weighting of internal predictive models instantiated by these functional modules ³⁴. One important corollary of modular 'disintegration' appears to be the broadening of the brain's functional repertoire of states or 'state-space' – commensurate with a broader or flatter global energy landscape ³⁵.

Here we hypothesize that the well-replicated finding of brain network disintegration and desegregation under psychedelics ^{36,37} will be apparent sub-acutely ³⁸, in post-treatment resting-state fMRI data. We also hypothesise that this effect, consistent with a flatter energy landscape, will relate to improved depression outcomes, and also that it will not be observed after a course of the selective serotonin reuptake inhibitor (SSRI), escitalopram.

Materials And Methods

Trial overviews

The trial designs for and the main clinical outcomes of the open-label ³¹ and DB-RCT ³² have been previously published. Both were conducted at the NIHR Imperial Clinical Research Facility and received Imperial College London Sponsorship, NHS research ethics favourable opinion, Health Research Authority and MHRA approval. This work was done under a UK Home Office Schedule 1 Drug Licence.

Participants

For both trials, eligibility required a general practitioner (GP) confirmed diagnosis of unipolar MDD (16+ on the 21-item Hamilton Depression Rating scale [HAM-D]). The open-label trial had the additional criteria of treatment-resistant depression, as no improvement despite multiple courses of antidepressant medication (mean = 4.6 ± 2.6 past medications, range = 2-11) ³⁹.

Exclusion criteria were: Immediate family or personal history of psychosis, risky physical health condition (physician-assessed), history of serious suicide attempts, positive pregnancy test and MRI contraindications. The DB-RCT had the additional exclusion criteria of selective serotonin reuptake inhibitor (SSRI) contraindications or previous escitalopram use. Eligible patients undertook telephone

screening interviews, provided written informed consent and their mental and physical medical histories were thoroughly evaluated.

Interventions

Patients in the open-label trial attended a 1-day pre-treatment baseline session that included eyes-closed resting-state fMRI and clinical assessment (Figure 1a). This was followed by two psilocybin therapy dosing days (DD), separated by 1 week. A low-dose of psilocybin (10mg) was orally ingested on DD1 and followed by a high-dose dose (25mg) on DD2. The follow-up fMRI and clinical assessment occurred one day after DD2. Patients attended an on-site clinical assessment at 1-week post-DD2 and completed further clinical assessment electronically at 3 and 6 months.

Of the 59 MDD patients in the DB-RCT, a random number generator allocated 30 to the 'psilocybin-arm' and 29 to the 'escitalopram-arm' (Figure 1b). Patients attended a pre-treatment baseline eyes-closed resting-state fMRI. DD1 consisted of either 25mg psilocybin (psilocybin-arm) or a presumed negligible 1mg psilocybin (escitalopram-arm) dose. All patients were informed that they would receive psilocybin but were blind to the dosage. DD2 occurred three weeks after DD1 and was a duplicate dosage. There was no dosage-crossover. Beginning one day post DD1, patients took daily capsules for 6 weeks and 1 day in total. For both conditions, one capsule per day was ingested for the first 3 weeks and two thereafter. Capsule content was either inert placebo (microcrystalline cellulose, psilocybin-arm) or escitalopram in the escitalopram-arm, 10mg for the first 3 weeks and 2 x 10mg = 20mg total thereafter.

Measuring depression severity

Beck Depression Inventory 1A (BDI-1A) scores were used to assess depression severity in both studies. This patient-rated measure captures a broader range of symptoms, with an additional focus on the cognitive features of depression, compared to other measures such as the QIDS-SR-16⁴⁰. In the open-label trial, BDI was measured at baseline and 1 week, 3 months and 6 months post DD2. For the DB-RCT, BDI was measured at baseline and 2, 4 and 6 weeks post DD1.

Measuring brain network modularity

For each scanning session, resting-state fMRI was recorded using a 3T Siemens Tim Trio MRI scanner at Invicro, London, UK (see Supplemental eMethods: MRI acquisition).

Our principal metric of interest was brain network modularity, a measure that describes the degree of segregation between the brain's functional networks (or, the communities of brain regions)⁴¹. Preprocessed fMRI data were used to estimate functional connectivity (FC) matrices from 100 cortical regions as defined by a functional atlas⁴² (see eMethods: MRI preprocessing; Functional connectivity) that were subjected to a commonly used community detection algorithm⁴³. This step seeks to maximise the extent to which the brain regions can be segregated into non-overlapping communities or modules⁴⁴.

See the Supplemental eMethods: Modularity section for details on modularity estimation and normalisation.

The modularity metric used in the present work has been applied in many previous contexts, including depression studies^{21,45,46}, where high modularity scores indicate a greater degree of separation between brain networks. Scores were compared between imaging sessions and correlated with depression severity scores.

Brain network characteristics

The modularity metric assesses a particular property of global brain function. To gain a finer-grained perspective on changes to individual networks, we employed methods from functional cartography⁴⁷. For study 1, we measured changes in *network recruitment* as the probability that brain regions of a network form communities with regions from the same network and *network integration* as the probability that regions form communities with regions from other networks (see eMethods: Functional cartography). For study 2, a dynamic community detection and flexibility analysis⁴⁸ was applied using a sliding-window approach where FC was estimated for multiple windows in time, instead of for the entire scan. Network flexibility was then defined by the average number of times that brain regions within a given network changed their community affiliation across time⁴⁷ (see eMethods: Dynamic flexibility).

Results

Open-label trial

Depression severity

Of the 19 patients recruited, 3 were excluded due to excessive fMRI head-motion. The remaining 16 patients (mean age=42.75, SD=10.15, 4 female) were the final analytical sample (Figure 2a). Baseline BDI scores indicated severe depression (mean BDI=34.81, SD=7.38). As previously reported, rapid and sustained reductions in depression severity were observed post-treatment³¹. Relative to baseline, significant BDI reductions were observed at 1 week (mean difference, -21.0 points; 95% CI, -27.30 to -14.71, $P<.001$) and this was still evident 6 months (mean difference, -14.19 points; 95% CI, -21.29 to -7.09, $P<.001$).

Decreased brain modularity following psilocybin therapy

Confirming our primary hypothesis prediction, brain network modularity was significantly reduced (Figure 3a) one day after psilocybin therapy (mean difference, -0.29; 95% CI 0.07 to 0.50, $P=.012$), indicative of an increased integration of brain networks.

Decreased modularity predicts long-term clinical outcomes

We hypothesised that decreased brain network modularity would relate to sustained improvements in depression severity following psilocybin therapy. To test this, we calculated Pearson correlations between the post-treatment brain modularity and the BDI scores from the 3 post-treatment timepoints (1 week, 3 months, 6 months). After false discovery rate (FDR) correction for multiple-comparisons, a strong significant correlation was observed at 6 months (Figure 3b - Pearson, $r=0.64$; $P=.023$). Although consistent with this, relationships at 3 months ($r=0.46$; $P=.114$) or 1 week ($r=0.29$; $P=.284$) did not survive correction. Furthermore, the pre vs post-treatment change in modularity significantly correlated with the change in BDI score at 6 months, relative to baseline (Figure 3c - Pearson, $r=0.54$; $P=.033$). These results indicate that decreased brain modularity relates to long-term improvements in depression symptom severity.

Decreased DMN & increased DMN-frontoparietal FC post-treatment

Consistent with previous work and our a priori assumptions, psilocybin therapy was related to significantly (FDR-corrected) decreased DMN network recruitment (Figure 3d - mean difference, -0.54; 95% CI, -0.92 to -0.15, $P=.009$), and increased integration between the DMN and multiple frontoparietal networks (DMN - EN, mean difference, 0.53; 95% CI, 0.15 to 0.90, $P=.01$; DMN - SN, mean difference, 0.55; 95% CI, 0.14 to 0.95, $P=.01$). A post-hoc exploratory analysis of network recruitment and integration indicated a general increase in DMN integration with other higher-order networks (Figure 3e).

Double-blind randomised controlled trial

Of the 59 MDD patients recruited, 29 were randomly allocated to the escitalopram-arm. Of those, 21 patients (mean age [SD], 40.9 [10.1], 6 [29%] female) were included in this imaging sample. 30 patients were randomly allocated to the psilocybin-arm. Of those, 22 patients (mean age [SD], 44.5 [11.0], 8 [36%] female) were included (Figure 2b).

Psilocybin therapy has greater efficacy than escitalopram for treating depression

Decreased depressive symptom severity was significantly greater under psilocybin than escitalopram, indicating superior efficacy of psilocybin therapy vs. escitalopram (Figure 4). This was confirmed within this neuroimaging sample by a significant arm x timepoint ANOVA interaction for the BDI scores ($F, 4.47$; $P=0.005$). FDR-corrected pairwise comparisons relative to baseline were significantly different at 2 weeks (mean difference, -8.73; 95% CI = -13.55 to -3.91, $P=0.002$), 4 weeks (mean difference, -7.79, 95% CI = -13.62 to -1.95, $P=0.013$) and at 6 weeks (mean difference, -8.78, 95% CI = -15.58 to -1.97, $P=0.013$), all favouring the psilocybin-arm (see ³² for full sample).

Increased brain network integration is specific to psilocybin therapy

Confirming our primary hypothesis (Figure 5a-b) and replicating the findings of the open-label trial, brain network modularity significantly reduced following psilocybin therapy (mean difference, -0.39; 95% CI =

-0.75 to -0.02, $P=0.039$). Individuals' decreases in brain network modularity significantly correlated with greater depression recovery at the 6-week primary endpoint (Pearson, $r=0.42$, $P=.025$, one-tailed).

Importantly, this replication was specific to the psilocybin-arm; in the escitalopram group (Figure 5d-e), modularity did not change from baseline to week 6 (mean difference, 0.01; -5% CI -0.35 to 0.33, $P=0.945$) and there was no significant relationship with changes in BDI scores (Pearson, $r=0.08$; $P=0.361$, one-tailed).

Depression recovery correlates with increased cognitive network flexibility.

Next, we examined the dynamic flexibility of the brain's canonical networks. This finer-grained metric summarises how often brain regions change their community allegiance during the course of an fMRI scan. Post-treatment change in network flexibility were correlated with the changes in BDI score. Specifically, increased EN dynamic flexibility related to greater depression recovery at the 6-week primary endpoint for the psilocybin-arm (Pearson, $r=-0.76$, $P=0.001$). Significant relationships predominantly involved the EN, SN and dorsal attention networks (Figure 5c). No significant correlations between BDI and dynamic flexibility were observed in the escitalopram-arm (Figure 5f).

Discussion

In light of growing evidence for the antidepressant efficacy of psilocybin therapy ³², these findings advance our understanding of possible underlying brain mechanisms. Across two trials decreased brain modularity was observed and correlated with improvements in depressive symptomatology. Moreover, this antidepressant action may be specific to psilocybin therapy, as no changes in modularity were observed with the conventional SSRI antidepressant, escitalopram.

Research into the acute brain action of psychedelics has revealed well-replicated changes in global brain function that are somewhat consistent with those observed here, i.e., an increased repertoire of inter-regional and between-network FC ^{35,36,49}. Our previous analysis had suggested some contrasting changes in the architecture of spontaneous brain function one day following psilocybin treatment for depression relative to what has been observed during the acute psychedelic state itself; i.e., spatially expanded DMN FC (post-treatment for TRD) versus acute DMN disintegration ³¹. Other teams have, however, reported some evidence suggestive of increased inter-network FC 1 week and 1-month post-psilocybin ⁵⁰, as well as 1-day post-ayahuasca ⁵¹, including consistent increases in DMN-SN FC ⁵¹, albeit in healthy volunteers. The present findings greatly extend on previous work however, by showing robust, reliable and treatment-specific decreases in brain modularity post psilocybin therapy for depression that relate to antidepressant efficacy.

The present modularity metrics may be more sensitive indices of the antidepressant action of psilocybin than previously applied time-averaged within and between-network FC analyses³¹. Indeed, they may bear relevance to other FC metrics applied to acute-state psychedelic fMRI data ^{35,36,49} where a general picture

of increased global FC and a broadened state-space has emerged ³⁴. In this context, the results could be understood as a ‘carryover’ effect resembling brain dynamics associated with the acute psychedelic state, albeit at an attenuated level and in a specific population (i.e., depressed patients).

Previous research on resting-state activity in depression has found abnormal community structure ⁵² and heightened network modularity ⁵³, correlating with symptom severity ^{21,54}. Additional work implies elevated FC between limbic regions such as the amygdala and high-level cortical regions in depression, correlating with ruminative symptoms ⁵⁵, as well as elevated within-DMN FC also correlating with rumination ¹⁹. Taken together, a model emerges of abnormally modular spontaneous brain function in depression that is effectively remediated by psilocybin therapy. According to various findings, the FC energy landscape or state-space in depression can be described as abnormally constricted, paralleling the narrow, internally focused, ruminative quality of mood and cognition in the disorder ¹³. In contrast, psilocybin therapy appears to expand the brain’s state-space, both acutely ⁵⁶ and, (as shown here), post-acutely in depressed patients, in a fashion that correlates with antidepressant outcomes. Moreover, this ‘liberating’ action of psilocybin is paralleled by subjective reports of emotional release via psychedelic therapy ^{57,58} as well as sub-acute increases in behavioural optimism ⁹, cognitive flexibility ⁵⁹, and psychological flexibility post psychedelic-use ^{60–62}.

We believe that this ‘liberating’ effect of psilocybin on cortical activity occurs via its direct agonist action on cortical 5-HT_{2A} receptors, dysregulating activity in regions rich in their expression. We believe chronic escitalopram does not have the same effect on brain modularity due to its more generalised action on the serotonin system and likely predominant effect on inhibitory postsynaptic 5-HT_{1A} receptors, which are richly expressed in limbic circuitry ^{33,63}.

Beyond the global decrease in network modularity post psilocybin, we observed functional changes in default mode, executive and salience network dynamics that are consistent with neurobiological models of depression ⁶⁴. These higher-order frontoparietal networks house the highest density of 5-HT_{2A} receptors, the principal action-site for serotonergic psychedelics ^{28,29}. High-level frontoparietal networks are implicated in the acute action of psychedelics, where they show reduced modularity and increased communication with regions ordinarily outside of their community limits ^{35–37,49}.

The EN and SN have been associated with tasks requiring cognitive flexibility such as, planning ⁶⁵, learning ⁶⁶ and task-switching ^{24,25}; impaired functioning of these networks have been reported in depression ^{21,53}, and other disorders exhibiting cognitive inflexibility such as traumatic brain injury ⁶⁷, autism spectrum disorder ⁶⁸ and obsessive-compulsive disorder ⁶⁹. Our results suggest that decreased modularity, or increased flexibility, of EN regions, following psilocybin therapy, is a key component of its therapeutic mechanism of action. We did not formally assess cognitive flexibility in the clinical trials reported here but we did observe improvements in general cognitive functioning post psilocybin treatment in the DB-RCT (see ³²).

Phase 3 clinical trials will be required to achieve licensing for psilocybin therapy and pragmatic trials will inform questions regarding treatment practicability and optimization⁷⁰. For brain imaging studies, we would recommend network modularity analyses like those employed here. fMRI datasets are burdensome and susceptible to noise, contributing to the challenge of detecting reliable biomarkers. Composite measures, such as network modularity, combined with a research domain, symptoms-based approach to psychological data, may be a productive way forward⁷⁰.

The dynamic flexibility analysis employed in the DB-RCT provided a useful perspective. However, it is limited by its requirement for fMRI scans with many timepoints. Timeseries need to be of sufficient length to be split into multiple time-windows that are themselves long enough to compute reliable FC measures. It can be challenging to reliably collect high-quality data of sufficient length in patient cohorts. Advances to fMRI temporal resolution, however, may improve this issue in the near future.

Conclusion

Depression presents considerable challenges to multiple stakeholders. Here, we identify a robust, reliable and potentially specific biomarker of response to psilocybin therapy for depression that may help to explain why it could become a valuable new treatment option.

Declarations

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References

1. World Health Organisation. *Depression and Other Common Mental Disorders: Global Health Estimates*. (World Health Organisation, 2017).
2. Tang, F. *et al.* COVID-19 related depression and anxiety among quarantined respondents. *Psychol. Health* **36**, 164–178 (2021).
3. Rabeea, S. A., Merchant, H. A., Khan, M. U., Kow, C. S. & Hasan, S. S. Surging trends in prescriptions and costs of antidepressants in England amid COVID-19. *DARU J. Pharm. Sci.* (2021) doi:10.1007/s40199-021-00390-z.
4. Hofmann, S. G., Curtiss, J., Carpenter, J. K. & Kind, S. Effect of treatments for depression on quality of life: a meta-analysis. *Cogn. Behav. Ther.* **46**, 265–286 (2017).

5. Locher, C. *et al.* Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis. *JAMA Psychiatry* **74**, 1011 (2017).
6. Haddad, P. The SSRI discontinuation syndrome. *J. Psychopharmacol. (Oxf.)* **12**, 305–313 (1998).
7. Steinert, C., Hofmann, M., Kruse, J. & Leichsenring, F. Relapse rates after psychotherapy for depression – stable long-term effects? A meta-analysis. *J. Affect. Disord.* **168**, 107–118 (2014).
8. Nutt, D. & Carhart-Harris, R. The Current Status of Psychedelics in Psychiatry. *JAMA Psychiatry* (2020) doi:10.1001/jamapsychiatry.2020.2171.
9. Lyons, T. & Carhart-Harris, R. L. More Realistic Forecasting of Future Life Events After Psilocybin for Treatment-Resistant Depression. *Front. Psychol.* **9**, 1721 (2018).
10. Rock, P. L., Roiser, J. P., Riedel, W. J. & Blackwell, A. D. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol. Med.* **44**, 2029–2040 (2014).
11. Beck, A. T. & Clark, D. A. Anxiety and depression: An information processing perspective. *Anxiety Res.* **1**, 23–36 (1988).
12. Holtzheimer, P. E. & Mayberg, H. S. Stuck in a rut: rethinking depression and its treatment. *Trends Neurosci.* **34**, 1–9 (2011).
13. Rolls, E. T. A non-reward attractor theory of depression. *Neurosci. Biobehav. Rev.* **68**, 47–58 (2016).
14. Hamilton, J. P., Farmer, M., Fogelman, P. & Gotlib, I. H. Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. *Biol. Psychiatry* **78**, 224–230 (2015).
15. Kendler, K. S. The Phenomenology of Major Depression and the Representativeness and Nature of DSM Criteria. *Am. J. Psychiatry* **173**, 771–780 (2016).
16. Nestler, E. J. *et al.* Neurobiology of Depression. *Neuron* **34**, 13–25 (2002).
17. Margulies, D. S. *et al.* Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proc. Natl. Acad. Sci.* **113**, 12574–12579 (2016).
18. Andrews-Hanna, J. R., Smallwood, J. & Spreng, R. N. The default network and self-generated thought: component processes, dynamic control, and clinical relevance: The brain's default network. *Ann. N. Y. Acad. Sci.* **1316**, 29–52 (2014).
19. Hamilton, J. P. *et al.* Default-Mode and Task-Positive Network Activity in Major Depressive Disorder: Implications for Adaptive and Maladaptive Rumination. *Biol. Psychiatry* **70**, 327–333 (2011).
20. Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D. & Pizzagalli, D. A. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. *JAMA Psychiatry* **72**, 603 (2015).
21. Lydon-Staley, D. M. *et al.* Repetitive negative thinking in daily life and functional connectivity among default mode, fronto-parietal, and salience networks. *Transl. Psychiatry* **9**, 234 (2019).
22. Ellard, K. K. *et al.* Functional Connectivity Between Anterior Insula and Key Nodes of Frontoparietal Executive Control and Salience Networks Distinguish Bipolar Depression From Unipolar Depression and Healthy Control Subjects. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* **3**, 473–484 (2018).

23. Beevers, C. Cognitive vulnerability to depression: A dual process model. *Clin. Psychol. Rev.* **25**, 975–1002 (2005).
24. Daws, R. E. *et al.* Optimisation of brain states and behavioural strategies when learning complex tasks. <http://biorxiv.org/lookup/doi/10.1101/2020.06.17.156570> (2020)
doi:10.1101/2020.06.17.156570.
25. Kim, C., Cilles, S. E., Johnson, N. F. & Gold, B. T. Domain general and domain preferential brain regions associated with different types of task switching: A Meta-Analysis. *Hum. Brain Mapp.* **33**, 130–142 (2012).
26. Turnbull, A. *et al.* Reductions in task positive neural systems occur with the passage of time and are associated with changes in ongoing thought. *Sci. Rep.* **10**, 9912 (2020).
27. Wilkinson, P. O. & Goodyer, I. M. Attention difficulties and mood-related ruminative response style in adolescents with unipolar depression. *J. Child Psychol. Psychiatry* **0**, 060907041921003-??? (2006).
28. Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F. I., Bäbler, A., Vogel, H. & Hell, D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action: *NeuroReport* **9**, 3897–3902 (1998).
29. Beliveau, V. *et al.* The structure of the serotonin system: A PET imaging study. *NeuroImage* **205**, 116240 (2020).
30. Andersen, K. A. A., Carhart-Harris, R., Nutt, D. J. & Erritzoe, D. Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatr. Scand.* **143**, 101–118 (2021).
31. Carhart-Harris, R. L. *et al.* Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Sci. Rep.* **7**, 13187 (2017).
32. Carhart-Harris, R. *et al.* Trial of Psilocybin versus Escitalopram for Depression. *N. Engl. J. Med.* **384**, 1402–1411 (2021).
33. Nutt, D., Erritzoe, D. & Carhart-Harris, R. Psychedelic Psychiatry's Brave New World. *Cell* **181**, 24–28 (2020).
34. Carhart-Harris, R. L. & Friston, K. J. REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacol. Rev.* **71**, 316–344 (2019).
35. Lord, L.-D. *et al.* Dynamical exploration of the repertoire of brain networks at rest is modulated by psilocybin. *NeuroImage* **199**, 127–142 (2019).
36. Luppi, A. I. *et al.* LSD alters dynamic integration and segregation in the human brain. *NeuroImage* **227**, 117653 (2021).
37. Carhart-Harris, R. L. *et al.* Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc. Natl. Acad. Sci.* **109**, 2138–2143 (2012).
38. Winkelman, M. Psychedelics as Medicines for Substance Abuse Rehabilitation: Evaluating Treatments with LSD, Peyote, Ibogaine and Ayahuasca. *Curr. Drug Abuse Rev.* **7**, 101–116 (2015).

39. Sackeim, H. A. The definition and meaning of treatment-resistant depression. *J. Clin. Psychiatry* **62 Suppl 16**, 10–17 (2001).
40. Fried, E. I. The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. *J. Affect. Disord.* **208**, 191–197 (2017).
41. Bassett, D. S. *et al.* Dynamic reconfiguration of human brain networks during learning. *Proc. Natl. Acad. Sci.* **108**, 7641–7646 (2011).
42. Schaefer, A. *et al.* Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb. Cortex* **28**, 3095–3114 (2018).
43. Blondel, V. D., Guillaume, J.-L., Lambiotte, R. & Lefebvre, E. Fast unfolding of communities in large networks. *J. Stat. Mech. Theory Exp.* **2008**, P10008 (2008).
44. Newman, M. E. J. Analysis of weighted networks. *Phys. Rev. E* **70**, 056131 (2004).
45. Zheng, H. *et al.* The dynamic characteristics of the anterior cingulate cortex in resting-state fMRI of patients with depression. *J. Affect. Disord.* **227**, 391–397 (2018).
46. Finc, K. *et al.* Dynamic reconfiguration of functional brain networks during working memory training. *Nat. Commun.* **11**, 2435 (2020).
47. Mattar, M. G., Cole, M. W., Thompson-Schill, S. L. & Bassett, D. S. A Functional Cartography of Cognitive Systems. *PLOS Comput. Biol.* **11**, e1004533 (2015).
48. Mucha, P. J., Richardson, T., Macon, K., Porter, M. A. & Onnela, J.-P. Community Structure in Time-Dependent, Multiscale, and Multiplex Networks. *Science* **328**, 876–878 (2010).
49. Roseman, L., Leech, R., Feilding, A., Nutt, D. J. & Carhart-Harris, R. L. The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. *Front. Hum. Neurosci.* **8**, (2014).
50. Barrett, F. S., Doss, M. K., Sepeda, N. D., Pekar, J. J. & Griffiths, R. R. Emotions and brain function are altered up to one month after a single high dose of psilocybin. *Sci. Rep.* **10**, 2214 (2020).
51. Pasquini, L., Palhano-Fontes, F. & Araujo, D. B. Subacute effects of the psychedelic ayahuasca on the salience and default mode networks. *J. Psychopharmacol. (Oxf.)* **34**, 623–635 (2020).
52. Lord, A., Horn, D., Breakspear, M. & Walter, M. Changes in Community Structure of Resting State Functional Connectivity in Unipolar Depression. *PLoS ONE* **7**, e41282 (2012).
53. Wei, M. *et al.* Abnormal dynamic community structure of the salience network in depression: Abnormal Salience Network in Depression. *J. Magn. Reson. Imaging* **45**, 1135–1143 (2017).
54. Ye, M. *et al.* Changes of Functional Brain Networks in Major Depressive Disorder: A Graph Theoretical Analysis of Resting-State fMRI. *PLOS ONE* **10**, e0133775 (2015).
55. Feurer, C. *et al.* Resting state functional connectivity correlates of rumination and worry in internalizing psychopathologies. *Depress. Anxiety* da.23142 (2021) doi:10.1002/da.23142.
56. Petri, G. *et al.* Homological scaffolds of brain functional networks. *J. R. Soc. Interface* **11**, 20140873 (2014).

57. Roseman, L. *et al.* Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory. *J. Psychopharmacol. (Oxf.)* **33**, 1076–1087 (2019).
58. Watts, R., Day, C., Krzanowski, J., Nutt, D. & Carhart-Harris, R. Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression. *J. Humanist. Psychol.* **57**, 520–564 (2017).
59. Murphy-Beiner, A. & Soar, K. Ayahuasca's 'afterglow': improved mindfulness and cognitive flexibility in ayahuasca drinkers. *Psychopharmacology (Berl.)* **237**, 1161–1169 (2020).
60. Zeifman, R. J. *et al.* Post-Psychedelic Reductions in Experiential Avoidance Are Associated With Decreases in Depression Severity and Suicidal Ideation. *Front. Psychiatry* **11**, 782 (2020).
61. Davis, A. K., Barrett, F. S. & Griffiths, R. R. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *J. Context. Behav. Sci.* **15**, 39–45 (2020).
62. Close, J. B., Hajien, E. C., Watts, R., Roseman, L. & Carhart-Harris, R. L. Psychedelics and psychological flexibility – Results of a prospective web-survey using the Acceptance and Action Questionnaire II. *J. Context. Behav. Sci.* **16**, 37–44 (2020).
63. Carhart-Harris, R. L. & Nutt, D. J. Serotonin and brain function: a tale of two receptors. *J. Psychopharmacol. Oxf. Engl.* **31**, 1091–1120 (2017).
64. Wang, X., Öngür, D., Auerbach, R. P. & Yao, S. Cognitive Vulnerability to Major Depression: View from the Intrinsic Network and Cross-network Interactions. *Harv. Rev. Psychiatry* **24**, 188–201 (2016).
65. Hampshire, A., MacDonald, A. & Owen, A. M. Hypoconnectivity and Hyperfrontality in Retired American Football Players. *Sci. Rep.* **3**, 2972 (2013).
66. Hampshire, A. *et al.* Probing cortical and sub-cortical contributions to instruction-based learning: Regional specialisation and global network dynamics. *NeuroImage* **192**, 88–100 (2019).
67. Hellyer, P. J., Scott, G., Shanahan, M., Sharp, D. J. & Leech, R. Cognitive Flexibility through Metastable Neural Dynamics Is Disrupted by Damage to the Structural Connectome. *J. Neurosci.* **35**, 9050–9063 (2015).
68. Watanabe, T. & Rees, G. Brain network dynamics in high-functioning individuals with autism. *Nat. Commun.* **8**, 16048 (2017).
69. Gu, B.-M. *et al.* Neural correlates of cognitive inflexibility during task-switching in obsessive-compulsive disorder. *Brain* **131**, 155–164 (2007).
70. Carhart-Harris, R. L. *et al.* Can pragmatic research, real-world data and digital technologies aid the development of psychedelic medicine? *Journal of Psychopharmacology* (2021).

Figures

Figure 1

Trial timeline schematics. a) Open-label trial. Eligible patients attended a baseline resting-state fMRI and clinical assessment visit. This was followed by two psilocybin therapy dosing days (DD) separated by 1 week, which differed in dose strength (DD1=10mg, DD2=25mg, oral psilocybin). The post-treatment fMRI scan occurred one day after DD2. Remote clinical assessment continued for 6 months. b) DB-RCT. Patients attended a baseline resting-state fMRI and clinical assessment visit and were randomly assigned to the psilocybin-arm (top-branch) or escitalopram arm (bottom-branch). The psilocybin-arm involved 2x25mg psilocybin therapy DD's with 3 weeks of daily placebo capsules following each DD. The escitalopram-arm involved 2x1mg psilocybin therapy DD's with 3 weeks of 10mg daily escitalopram following DD1 and 20mg of escitalopram following DD2. Both groups attended a post-treatment fMRI and clinical assessment visit 6 weeks and one day after DD1.

Figure 2

Recruitment flow diagram for the open-label (a) and DB-RCT (b).

Figure 3

Open-label trial: Treatment-resistant depression patient responses to psilocybin therapy relate to decreases in brain network modularity one day post-treatment. a) Brain modularity (Q - normalised) significantly reduced, indicating a global increase in brain network integration. The solid and dotted lines represent the mean and median, respectively. Patient's data are connected by solid lines and rendered red if modularity decreased. b) Absolute post-treatment scan modularity correlated with absolute Beck

depression inventory (BDI) scores at 6 months post-treatment. c) Change in brain modularity after treatment significantly correlated with the change in BDI scores between baseline and at 6 months. d) DMN recruitment decreased and its integration with the EN (gold) and SN (purple) increased (bars represent the standard error of the mean) following psilocybin therapy. e) Paired t-statistics of the change in network recruitment (diagonal) and between network integration (off-diagonal). This exploratory analysis uses an uncorrected $P < .05$ threshold (Red=increase, Blue=Decrease). Comparisons do not survive multiple comparisons correction. DMN=Default Mode Network, DA=Dorsal attention, EN=Executive Network, LI=Limbic, SM=Somatomotor, SN=Salience Network, VS=Visual.

Figure 4

DB-RCT: Beck depression inventory (BDI) scores from each study arm. a) Boxplot for each timepoint at which BDI scores were measured. Decreases in depression severity from baseline were significantly greater in the psilocybin-arm (red) than in the escitalopram-arm (blue) at each timepoint. Median values are represented by the central marks, the 25th and 75th percentiles by the box edges and the whiskers extend to the data range. b) Individual patient BDI scores in a raster plot. Each row represents a single patient, each column represents a timepoint (BL=Baseline, wk=week). Rows were ordered by each patient's total BDI score sum across timepoints. Black/grey=Severe depression, white/light grey=Mild to no depression.

Figure 5

DB-RCT: Brain modularity reductions and individual differences are specific to psilocybin treatment. a) Significant decreases in brain network modularity (Q - normalised) in the psilocybin-arm post-treatment. The solid and dotted lines on the distributions represent the mean and median, respectively. Individual patient data are represented, connected with solid lines between sessions which were rendered red if modularity decreased between sessions. b) Patient individual differences (relative to baseline) correlate with improved treatment response at the 6-week primary endpoint. c) Significant correlations between changes in dynamic network flexibility and BDI (relative to baseline) at 6 weeks are coloured and those that survive FDR-correction are denoted with a * (white = $P>.05$). The equivalent analyses in the escitalopram-arm did not show significant session differences in brain modularity (e) and individual differences in BDI at 6 weeks (relative to baseline) did not correlate with modularity changes (e) or network flexibility (f). DN=Default Mode Network, DA=Dorsal attention, EN=Executive network, LI=Limbic, SM=Somatomotor, SN=Salience Network VS=Visual.

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