Psychedelic science in post-COVID-19 psychiatry

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The medium- to long-term consequences of COVID-19 are not yet known, though an increase in mental health problems are predicted. Multidisciplinary strategies across socio-economic and psychological levels may be needed to mitigate the mental health burden of COVID-19. Preliminary evidence from the rapidly progressing field of psychedelic science shows that psilocybin therapy offers a promising transdiagnostic treatment strategy for a range of disorders with restricted and maladaptive habitual patterns of cognition and behaviour, notably depression, addiction and obsessive compulsive disorder. The COMPASS Pathways (COMPASS) phase 2b double-blind trial of psilocybin therapy in antidepressant-free, treatment-resistant depression (TRD) is underway to determine the safety, efficacy and optimal dose of psilocybin. Results from the Imperial College London Psilodep-RCT comparing the efficacy and mechanisms of action of psilocybin therapy to the selective serotonin reuptake inhibitor (SSRI) escitalopram will soon be published. However, the efficacy and safety of psilocybin therapy in conjunction with SSRIs in TRD is not yet known. An additional COMPASS study, with a centre in Dublin, will begin to address this question, with potential implications for the future delivery of psilocybin therapy. While at a relatively early stage of clinical development, and notwithstanding the immense challenges of COVID-19, psilocybin therapy has the potential to play an important therapeutic role for various psychiatric disorders in post-COVID-19 clinical psychiatry.

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Crisis induce a wide range of psychological reactions, with varying degrees of adaptability. The combination of uncertainty and social distancing induced by the COVID-19 pandemic can lead to excessive fear/ anxiety, loneliness and depressive thoughts (Holmes et al. 2020, Luykx et al. 2020, Vindegaard & Benros, 2020). While the medium- to long-term mental health consequences are not yet known, an increase in psychological and psychiatric problems are predicted (Horesh & Brown, 2020, O’Connor et al. 2020, Türközer & Öngür, 2020), with an excess burden on vulnerable groups (Kelly, 2020). The implementation of a range of multidisciplinary strategies across socio-economic and psychological levels may be needed to mitigate the mental health burden of COVID-19.

Accumulating clinical data shows that psilocybin therapy may be an effective therapeutic strategy across a range of disorders, including depression (Carhart-Harris et al. 2016, Davis et al. 2019), obsessive compulsive disorder (Moreno et al. 2006) and addiction disorders (Garcia-Romeu et al. 2019, Johnson et al. 2017). In addition, clinical trials are underway to investigate psilocybin therapy in anorexia nervosa (NCT04052568) and there may be a role for psilocybin therapy in the treatment of anxiety disorders (Weston et al. 2020).

Recent advances in psychedelic science are gradually unravelling the multimodal mechanisms underlying the therapeutic effect of psilocybin therapy (for example Carhart-Harris & Friston, 2019, Lord et al. 2019, Peller et al. 2020, Varley et al. 2020). Psilocybin reliably alters an individual’s state of consciousness, probably through agonist mechanisms at the 5-HT2A receptor, especially in the deep pyramidal cells in the cortex (Nutt et al. 2020). The transient, dose-dependent alteration of the complex interconnected neural networks of the brain (Lord et al. 2019, Varley et al. 2020) encompassing the self-reflecting ‘ego’, induced by psilocybin, can lead to profound experiences of connectivity to others and the environment (Erritzoe et al. 2018, Griffiths et al. 2006, 2016, Grob et al. 2011, Kettner et al. 2019, Smigielski et al. 2019) and can be harnessed by psilocybin therapy to re-conceptualise restricted and maladaptive habitual patterns of cognition and behaviour.
As such, psilocybin therapy provides a translatable, transdiagnostic treatment strategy that can be further refined by a precise-personalised approach (Kelly et al. 2017, Lewis et al. 2020, Peller et al. 2016, 2020, Studerus et al. 2012). Advancing precise-personalised psilocybin therapy is of particular importance given the individual variation in responses, high rates of relapse in psychiatric disorders and contraindication in psychotic and manic conditions (Carhart-Harris et al. 2018). It has been suggested that internalising disorders may be a useful broad construct for the therapeutic application of psilocybin therapy (Nutt & Carhart-Harris, 2020). Moreover, given the transdiagnostic potential, a dimensional framework (Insel, 2014) that aligns with bio-psycho signatures could also be leveraged to enhance the targeted application of psilocybin therapy and further unravel the mechanisms underpinning the acute and persistent therapeutic effects. Indeed, further exploration of psilocybin’s impact on neuroimmunoendocrine pathways (Galvão et al. 2018, Hasler et al. 2004, Nau et al. 2013, Strajhar et al. 2016, Szabo, 2015), including the microbiome–gut–brain axis, may provide additional insights into the persisting therapeutic effects (Kelly et al. 2019c, Kuypers, 2019).

Notwithstanding the limitations of animal models in fully capturing the different aspects of psilocybin therapy (Jefsen et al. 2019, Meinhardt et al. 2020), preclinical data have shown that serotonergic psychedelics, including psilocybin, can induce hippocampal neurogenesis (Catlow et al. 2013, Morales-Garcia et al. 2017, Vaidya et al. 1997), promote dendritic spine growth and stimulate synapse formation in the prefrontal cortex (González-Maeso et al. 2007, Ly et al. 2018). Preclinical data also suggest that psychedelics lead to 5-HT2A receptor-mediated glutamate release (Ly et al. 2018), and a recent magnetic resonance spectroscopy study in healthy humans found that psilocybin administration was associated with increased glutamate in the medial prefrontal cortex (Mason et al. 2020).

Researchers from the Center for Psychedelic and Consciousness Research at Johns Hopkins University recently focussed on the claustrum, a thin sheet of grey matter, embedded in the white matter of the cerebral hemispheres and situated between the putamen and the insular cortex, with a rich supply of 5-HT2A receptors and glutamatergic connectivity to the cerebral cortex, and thought to be associated with cognitive task switching (Barrett et al. 2020b, Krimmel et al. 2019). Psilocybin acutely reduced claustrum activity and altered its connectivity with the default mode network and frontoparietal task control network, in a study involving 15 healthy volunteers, thus implicating this region as a key mediator in psilocybin therapy (Barrett et al. 2020b).

The same research group, in an open-label pilot study of 12 healthy volunteers, showed that psilocybin reduced both negative affect and amygdala responses to emotional stimuli 1 week after psilocybin, whereas by 1 month after psilocybin the responses returned to baseline (Barrett et al. 2020a). At both 1 week and 1 month after psilocybin, there were global increases in brain functional connectivity (Barrett et al. 2020a). A previous study in healthy controls also showed reduced amygdala reactivity, particularly on the right side, to negative and neutral stimuli due to psilocybin (Kraehenmann et al. 2015). In contrast, an open-label study of 19 subjects with treatment-resistant depression (TRD) showed that psilocybin increased amygdala responses to emotional faces (Roseman et al. 2018) and decreased functional connectivity between the ventromedial prefrontal cortex and the right amygdala 1 day after psilocybin (Mertens et al. 2020). Larger studies may be needed to resolve the complexities.

In the midst of this evolving ‘Psychedelic Revolution in Psychiatry’ (Nutt et al. 2020) and potential increasing recreational psychedelic use, albeit from 0.55% in 2015 to 0.86% in 2018, in a sample of 168,000 members of the public (Yockey et al. 2020), the Royal Australian and New Zealand College of Psychiatrists (RANZCP) recently published a clinical memorandum on the ‘Therapeutic use of psychedelic substances’ (RANZCP, 2020). This memorandum acknowledges not only the emerging therapeutic potential of psychedelics but also the need for more efficacy and safety data, particularly on potential long-term effects, to inform future potential use in psychiatric practice.

In terms of acceptability and tolerability, results from the Global Drug Survey (2019) of 85,000 people showed only 18% of those surveyed, who have never used psychedelics, said they would accept psilocybin therapy for depression or PTSD, increasing to 59% in those who had previously tried psychedelics (Winstock & Johnson, 2019). The reported fears related to ‘brain damage and bad trips’ (Winstock & Johnson, 2019). Psilocybin therapy data from John Hopkins University, over a 16-year period, encompassing 250 volunteers and 380 sessions, reported no major psychological issues, with 0.9% of volunteers experiencing minor and transient psychological issues (Carbonaro et al. 2016). However, high-quality clinical data on the long-term effects of psychedelics are lacking. For example, there is very limited data on hallucinogen-persisting perception disorder (HPPD), a rare condition that involves the continued presence of sensory disturbances (Halpern et al. 2018; Martinotti et al. 2018; Orsolini et al. 2017). A review by Halpern and colleagues suggests that HPPD is, in most cases, due to a ‘subtle over-activation of predominantly neural visual pathways that worsens anxiety after ingestion of
arousal-altering drugs, including non-hallucinogenic substances’ (Halpern et al. 2018). The authors note that a personal or family history of anxiety and pre-drug use complaints of tinnitus, eye floaters and concentration problems may predict vulnerability for HPPD (Halpern et al. 2018). Similarly, the impact of regular psychedelic use on the brain is limited (Bouso et al. 2015; Halpern et al. 2005). Although, it is important to note that psilocybin therapy studies do not use regular dosing, using between 1 and at most 3 doses of psilocybin.

Dublin is one of the clinical trial centres participating in a double-blind randomised controlled phase 2b COMPASS trial of psilocybin therapy in TRD (COMP001) (Kelly et al. 2019a). Results from this large scale trial, and others, will address concerns regarding psilocybin safety, efficacy and dose optimisation. Moreover, we eagerly await the results from the potentially paradigm shifting, double-blind trial of psilocybin therapy versus the selective serotonin reuptake inhibitor (SSRI) escitalopram in depression from the Centre for Psychedelic Research at Imperial College London (Psilodep-RCT, NCT03429075) (Nutt & Carhart-Harris, 2020) and acknowledge that for some people with depression, SSRIs and psilocybin may become ‘competitive options’ despite postulated mechanistic complementarity, with SSRIs enhancing 5-HT1AR pathway and psilocybin enhancing the 5-HT2AR pathway (Carhart-Harris & Nutt, 2017). However, many people with depression may choose to remain on antidepressants (Kelly et al. 2019b) and it is important to determine the safety and efficacy of this approach. 5-HT2AR antagonists, such as ketanserin, block the therapeutic effect of psilocybin (Preller et al. 2017), whereas the partial 5-HT1A agonist buspirone may exert inhibitory effects (Pokorny et al. 2016). However, apart from anecdotal evidence suggesting a blunted effect (Bonson et al. 1996; Bonson & Murphy, 1996), psilocybin therapy in conjunction with SSRIs has never been investigated in TRD.

The gradual emergence from COVID-19 lockdown will see the launch of a new COMPASS clinical study (COMP003) in Dublin and San Diego to determine the antidepressant effect of psilocybin therapy in people with TRD who continue SSRI medication. This exploratory open-label trial will aim to recruit 20 participants with a single or recurrent episode of at least moderate clinical depression between 3 months and 2 years duration that has not responded to an adequate dose and duration of at least two pharmacological treatments. A single dose of oral psilocybin of 25mg will be administered with psychological support to participants who have been taking an SSRI’s for at least 6 weeks. The results of this study could have important practical implications for the future of psilocybin therapy and may have implications for future phase 3 trials in TRD, which could pave the way for the integration of psilocybin therapy into clinical psychiatry.

However, both clinical and research psychiatry have been transformed by COVID-19, demanding additional strategies to overcome the considerable challenges (O’Brien & McNicholas, 2020; Türközer & Öngür, 2020). To mitigate the spread of COVID-19 and facilitate the safe reopening and progress of ongoing psilocybin trials, in line with local and national guidelines, a number of measures will be implemented. These include, for example, participant and researcher respiratory symptom checklists, regular temperature checks, access to COVID-19 testing (if indicated), meticulous attention to extra hygiene measures, personal protective equipment (where not expected to negatively impact the participant’s experience), and the option of remote study visits (where possible by the protocol). Notwithstanding the challenges and the early stage of clinical development, psilocybin therapy, at the forefront of translational neuroscience and psychiatry, is likely to play an important therapeutic role for certain conditions in post-COVID-19 clinical psychiatry.

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Conflict of interest

Authors have no conflicts of interest to disclose.

Ethical standards

The Cork Clinical Research Ethics Committee approved COMP001 and COMP003. The authors assert that all procedures contributing to this work comply with the ethical standards of the Cork Clinical Research Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2008.

References

Barrett FS, Doss MK, Sepeda ND, Pekar JJ, Griffiths RR (2020a). Emotions and brain function are altered up to one month after a single high dose of psilocybin. Scientific Reports 10, 2214.

Barrett FS, Krimmel SR, Griffiths R, Seminowicz DA, Mathur BN (2020b). Psilocybin acutely alters the functional connectivity of the claustrum with brain networks that support perception, memory, and attention. Neuroimage, 116980.

Bonson KR, Buckholts JW, Murphy DL (1996). Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. Neuropsychopharmacology 14, 425–436.
Bouso JC, Palhano-Fontes F, Rodríguez-Fornells A, Ribeiro S, Sanches R, Crippa JAS, Hallak JEC, de Araújo DB, Riba J (2015). Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. European Neuropsychopharmacology 25, 483–492.

Carbonaro TM, Bradstreet MP, Barrett FS, MacLean KA, Jesse R, Johnson MW, Griffiths RR (2016). Survey study of challenging experiences after ingesting psilocybin mushrooms: acute and enduring positive and negative consequences. Journal of Psychopharmacology 30, 1268–1278.

Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, Kaelen M, Giribaldi B, Bloomfield M, Pilling S, Rickard JA, Forbes B, Feilding A, Taylor D, Curran HV, Nutt DJ (2018). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl) 235, 399–408.

Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D, Pilling S, Curran VH, Nutt DJ (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3, 619–627.

Carhart-Harris RL, Friston KJ (2019). REBUS and the anarchic brain: toward a unified model of the brain action of psychedelics. Pharmacological Review 71, 316–344.

Carhart-Harris RL, Nutt DJ (2017). Serotonin and brain function: a tale of two receptors. Journal of Psychopharmacology 31, 1091–1120.

Catlow BJ, Song S, Paredes DA, Kirstein CL, Sanchez-Ramos J (2013). Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning. Experimental Brain Research 228, 481–491.

Davis AK, May DG, Cosimano M, Johnson MW, Barrett FS, Griffiths RR (2019). Psilocybin-assisted psychotherapy for the treatment of Major Depressive Disorder: Preliminary results from a randomized controlled trial. In American Psychiatric Association CONVENTION Annual Meeting.

Erritzoe D, Roseman L, Nour MM, MacLean K, Kaelen M, Nutt DJ, Carhart-Harris RL (2018). Effects of psilocybin therapy on personality structure. Acta Psychiatrica Scandinavica 138, 368–378.

Galvão, ACM de Almeida RN, Silva E, Freire FAM, Palhano-Fontes F, Onias H, Arcorède E, Maia-de-Oliveira JP, de Araújo DB, Lobão-Soares B, Galvão-Coelho NL (2018). Cortisol modulation by ayahuasca in patients with treatment resistant depression and healthy controls. Front Psychiatry 9, 185.

Garcia-Romeu A, Davis AK, Erowid F, Erowid E, Griffiths RR, Johnson MW (2019). Cessation and reduction in alcohol consumption and misuse after psychedelic use. Journal of Psychopharmacology 33, 1088–1101.

González-MaesO J, Weisstaub NV, Zhou M, Chan P, IviC L, Ang R, Lira A, Bradley-Moore M, Ge, Y, Zhou Q, Sealfon SC, Gingrich JA (2007). Hallucinogens recruit specific cortical 5-HT2A receptor-mediated signaling pathways to affect behavior. Neuron 53, 439–452.

Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. Journal of Psychopharmacology (Oxford, England) 30, 1181–1197.

Griffiths RR, Richards WA, McCann U, Jesse R (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl) 187, 268–283; discussion 284–292.

Grobs CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer GR (2011). Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Psilocybin for anxiety in advanced-stage cancer. JAMA Psychiatry 68, 71–78.

Halpern JH, Lerner AG, Passie T (2018). A review of hallucinogen persisting perception disorder (HPPD) and an exploratory study of subjects claiming symptoms of HPPD. Current Topics in Behavioral Neurosciences 36, 333–360.

Halpern JH, Sherwood AR, Hudson JJ, Yurgelun-Todd D, Pope HG, Jr. (2005). Psychological and cognitive effects of long-term peyote use among Native Americans. Biological Psychiatry 58, 624–631.

Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX (2004). Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. Psychopharmacology (Berl) 172, 145–156.

Holmes EA, O’Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, Ballard C, Christensen H, Cohen Silver R, Everall I, Ford T, John A, Kabir T, King K, Madan I, Michie S, Przybyslki AK, Shafran R, Sweeney A, Worthman CM, Yardley L, Cowan K, Cope C, Hotopf M, Bullmore E (2020). Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry 7, 547–560.

Horesh D, Brown AD (2020). Traumatic stress in the age of COVID-19: a call to close critical gaps and adapt to new realities. Psychological Trauma 12, 331–335.

Insel TR (2014). The NIMH Research Domain Criteria (RDoC) project: precision medicine for psychiatry. American Journal of Psychiatry 171, 395–397.

Jepsen O, Hoijgaard K, Christiansen SL, Elving B, Nutt DJ, Wegener G, Müller HK (2019). Psilocybin lacks antidepressant-like effect in the Flinders Sensitive Line rat. Acta Neuropsychiatrica 31, 213–219.

Johnson MW, Garcia-Romeu A, Griffiths RR (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. The American Journal of Drug and Alcohol Abuse 43, 55–60.
Kelly BD (2020). Coronavirus disease: challenges for psychiatry. British Journal of Psychiatry 217, 352–353.

Kelly JR, Baker A, Babiker M, Burke L, Brennan C, O’Keane V (2019a). The psychedelic renaissance: the next trip for psychiatry? Irish Journal of Psychological Medicine, 1–5.

Kelly JR, Clarke G, Cryan JF, Dinan TG (2017). Dimensional thinking in psychiatry in the era of the Research Domain Criteria (RDoC). Irish Journal of Psychological Medicine 35, 89–94.

Kelly JR, Cosgrove M, Judd C, Scott K, Loughlin AM, O’Keane V (2019b). Mood matters: a national survey on attitudes to depression. Irish Journal of Medical Science 188, 1317–1327.

Kelly JR, Keane VO, Cryan JF, Clarke G, Dinan TG (2019c). Mood and microbes: gut to brain communication in depression. Gastroenterology Clinics of North America 48, 389–405.

Kettner H, Gandy S, Hajen E, Carhart-Harris RL (2019). From Egoism to Ecocism: psychedelics increase nature relatedness in a state-mediated and context-dependent manner. International Journal of Environmental Research and Public Health 16.

Kraehenmann R, Preller KH, Scheidegger M, Pokorny T, Bosch OG, Seifritz E, Vollenweider FX (2015). Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. Biological Psychiatry 78, 572–581.

Kriemel SR, White MG, Panicker MH, Barrett FS, Mathur BN, Seminowicz DA (2019). Resting state functional connectivity and cognitive task-related activation of the human claustrum. Neuroimage 196, 59–67.

Kuypers KPC (2019). Psychedelic medicine: the biology underlying the persisting psychedelic effects. Med Hypotheses 125, 21–24.

Lewis CR, Preller KH, Braden BB, Riecken C, Vollenweider FX (2020). Rostral anterior cingulate thickness predicts the emotional psilocybin experience. Biomedicines 8, 34.

Lord LD, Expert P, Atasoy S, Roseman L, Rapuano K, Lambotte R, Nutt DJ, Deco G, Carhart-Harris RL, Kringlebach ML, Cabral J (2019). Dynamical exploration of the repertoire of brain networks at rest is modulated by psilocybin. Neuroimage 199, 127–142.

Luyxk JJ, Vinkers CH, Tijdink JK (2020). Psychiatry in times of the coronavirus disease 2019 (COVID-19) pandemic: an imperative for psychiatrists to act now. JAMA Psychiatry.

Ly, C, Greb AC, Cameron LP, Wong JM, Barragan EV, Wilson PC, Burbach KF, Soltanzadeh Zarandi S, Sood A, Paddy MR, Duim WC, Dennis MY, McAllister AK, Ori-McKenney KM, Gray JA, Olson DE (2018). Psychedelics promote structural and functional neural plasticity. Cell Reports 23, 3170–3182.

Martinotti G, Santacroce R, Pettoruso M, Montemirito C, Spano MC, Lorusso M, di Giannantonio M, Lerner AG (2018). Hallucinogen persisting perception disorder.

etiology, clinical features, and therapeutic perspectives. Search Results 8.

Mason NL, Kuypers KPC, Müller F, Reckweg J, Tse DHY Toennes SW, Hutten N, Jansen JFA, Stiers P, Feilding A, Ramaekers JG (2020). Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin. Neuropsychopharmacology.

Meinhardt MW, Güngör, C, Skorodumov I, Mertens LJ, Spanagar R (2020). Psilocybin and LSD have no long-lasting effects in an animal model of alcohol relapse. Neuropsychopharmacology 45, 1316–1322.

Mertens LJ, Wall MB, Roseman L, Demetriou L, Nutt DJ, Carhart-Harris RL (2020). Therapeutic mechanisms of psilocybin: changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. Journal of Psychopharmacology 34, 167–180.

Morales-Garcia JA, de la Fuente Revenga M, Alonso-Gil S, Rodriguez-Franco MI, Feilding A, Perez-Castillo A, Riba J (2017). The alkaloids of Banisteriopsis caapi, the plant source of the Amazonian hallucinogen Ayahuasca, stimulate adult neurogenesis in vitro. Scientific Reports 7, 5309.

Moreno FA, Wiegand CB, Taitano EK, Delgado PL (2006). Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. Journal of Clinical Psychiatry 67, 1735–1740.

Nau F, Jr., Yu, B, Martin D, Nichols CD (2013). Serotonin 5-HT2A receptor activation blocks TNF-α mediated inflammation in vivo. PLOS ONE 8, e75426.

Nutt D, Carhart-Harris R (2020). The current status of psychedelics in psychiatry. JAMA Psychiatry.

Nutt D, Erritzoe D, Carhart-Harris R (2020). Psychedelic psychiatry’s brave new world. Cell 181, 24–28.

O’Brien M, McNicholas F (2020). The use of telepsychiatry during COVID-19 and beyond. Irish Journal of Psychological Medicine, 1–17.

O’Connor K, Wrigley M, Jennings R, Hill M, Niazi A (2020). Mental Health Impacts of COVID-19 in Ireland and the Need for a Secondary Care, Mental Health Service Response. Irish Journal of Psychological Medicine, 1–18.

Orsolini L, Papanti GD, De Berardis D, Guirguis A, Corkery JM, Schifano F (2017). The “Endless Trip” among the NPS users: psychopathology and psychopharmacology in the hallucinogen-persisting perception disorder. A systematic review. Front Psychiatry 8, 240.

Pokorny T, Preller KH, Kraehenmann R, Vollenweider FX (2016). Modulatory effect of the 5-HT1A agonist buspirone and the mixed non-hallucinogenic 5-HT1A/2A agonist ergotamine on psilocybin-induced psychedelic experience. European Neuropsychopharmacology 26, 756–766.

Preller KH, Duerler P, Burt JB, Ji, JL, Adkinson B, Stämpfli P, Seifritz E, Repovš, G, Krystal JH, Murray JD, Anticevic A, Vollenweider FX (2020). Psilocybin induces time-dependent changes in global functional connectivity. Biological Psychiatry 88, 197–207.
Preller KH, Herdener M, Pokorny T, Planzer A, Kraehemann R, Stämpfli P, Liechti ME, Seifritz E, Vollenweider FX (2017). The fabric of meaning and subjective effects in LSD-induced states depend on Serotonin 2A receptor activation. *Current Biology* **27**, 451–457.

Preller KH, Pokorny T, Hock A, Kraehemann R, Stämpfli P, Seifritz E, Scheidegger M, Vollenweider FX (2016). Effects of serotonin 2A/1A receptor stimulation on social exclusion processing. *Proceedings of the National Academy of Sciences of the United States of America* **113**, 5119–5124.

RANZCP (2020). The Royal Australian and New Zealand College of Psychiatrists (RANZCP). Therapeutic use of psychedelic substances.

Roseman I, Demetriou L, Wall MB, Nutt DJ, Carhart-Harris RL (2018). Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. *Neuropsychopharmacology* **42**, 263–269.

Smigielski L, Scheidegger M, Kometer M, Vollenweider FX (2019). Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects. *Neuroimage* **196**, 207–215.

Strajhar P, Schmid Y, Liakoni E, Dolder PC, Rentsch KM, Kratschmar DV, Odermatt A, Liechti ME (2016). Acute effects of lysergic acid diethylamide on circulating steroid levels in healthy subjects. *J Neuroendocrinol* **28**, 12374.

Studerus E, Gamma A, Kometer M, Vollenweider FX (2012). Prediction of psilocybin response in healthy volunteers. *PLoS One* **7**, e30800.

Szabo A (2015). Psychedelics and Immunomodulation: Novel Approaches and Therapeutic Opportunities. *Frontiers in Immunology* **6**, 358.

Türközer HB, Öngür, D (2020). A projection for psychiatry in the post-COVID-19 era: potential trends, challenges, and directions. *Mol Psychiatry*, 1–6.

Vaidya VA, Marek GJ, Aghajanian GK, Duman RS (1997). 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. *J Neurosci* **17**, 2785–2795.

Varley TF, Carhart-Harris R, Roseman L, Menon DK, Stamatakis EA (2020). Serotonergic psychedelics LSD & psilocybin increase the fractal dimension of cortical brain activity in spatial and temporal domains. *Neuroimage* **220**, 117049.

Vindegaard N, Benros ME (2020). COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. *Brain, Behavior, and Immunity*, S0889-1591(20)30954-5.

Weston NM, Gibbs D, Bird CIV Daniel A, Jelen LA, Knight G, Goldsmith D, Young AH, Rucker JJ (2020). Historic psychedelic drug trials and the treatment of anxiety disorders. *Depress Anxiety*.

Winstock AR, Johnson MW (2019). Global Drugs Survey: The psychedelic revolution in psychiatry and why patient opinion matters so much. https://www.globaldrugsurvey.com/gds-2019/gds2019-the-psychedelic-revolution-in-psychiatry-and-why-patient-opinion-matters-so-much/

Yockey RA, Vidourek RA, King KA (2020). Trends in LSD use among US adults: 2015–2018. *Drug and Alcohol Dependence* **212**, 108071.