

Psychedelics and the essential importance of context

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Journal of Psychopharmacology
2018, Vol. 32(7) 725–731
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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0269881118754710
journals.sagepub.com/home/jop



Abstract

Psychedelic drugs are making waves as modern trials support their therapeutic potential and various media continue to pique public interest. In this opinion piece, we draw attention to a long-recognised component of the psychedelic treatment model, namely ‘set’ and ‘setting’ – subsumed here under the umbrella term ‘context’. We highlight: (a) the pharmacological mechanisms of classic psychedelics (5-HT_{2A} receptor agonism and associated plasticity) that we believe render their effects exceptionally sensitive to context, (b) a study design for testing assumptions regarding positive interactions between psychedelics and context, and (c) new findings from our group regarding contextual determinants of the quality of a psychedelic experience and how acute experience predicts subsequent long-term mental health outcomes. We hope that this article can: (a) inform on good practice in psychedelic research, (b) provide a roadmap for optimising treatment models, and (c) help tackle unhelpful stigma still surrounding these compounds, while developing an evidence base for long-held assumptions about the critical importance of context in relation to psychedelic use that can help minimise harms and maximise potential benefits.

Keywords

Psychedelics, psychotherapy, serotonin

We are currently witnessing a renaissance in psychedelic research; so much so, that phrases like this are beginning to feel platitudinal. Some have referred to the present resurgence as a ‘third wave’ (Austin et al. 2017), since this is not the first time psychedelics have brightened the fields of psychology and psychiatry (Carhart-Harris and Goodwin, 2017), and certain indigenous cultures – most notably in the Americas – have celebrated their effects since ancient times (Labate, 2014; Labate and Cavnar, 2016). Given the promising nature of the current psychedelic research climate, it feels sensible to draw attention to potential pitfalls, so as to protect against them. The main hypothesis of this article is that the therapeutic action of psychedelics is *fundamentally reliant on context* – both in the psychological and environmental sense. It is argued that neglect of context could render a psychedelic experience not only clinically ineffective but also potentially harmful – accounting, in part, for the negative stigma that still shackles these drugs (Erritzoe et al., 2017; Erritzoe and Richards, 2017).¹

Beginning chronologically, ceremonial use of psychedelics among indigenous people has historically placed, and still continues to place, great emphasis on environmental context and psychological factors brought to the experience, such as having a clear intention and an open, enquiring attitude, as well as the importance of ceremony, ritual, and song (Labate, 2014; Loizaga-Velder and Verres, 2014; Nettl, 1956; Tupper and Labate, 2014). Indigenous approaches are often animistic in nature, for example, ascribing a healing sentience to the relevant psychedelic plant(s), special powers to the guiding shaman and a locus of therapeutic action to the chants (icaros) sung to the recipient(s) (Dobkin de Rios, 2009). Some adherents of the indigenous model consider neglect of these components disrespectful, and sensitivities exist regarding the appropriation of indigenous methods by Westerners (Feinberg, 2017; Schwartz, 2017), although a ready willingness

to adapt to Western preferences can also be seen among certain indigenous practitioners (Feinberg, 2017; Labate, 2014).

Moving into the 1950–60s and the first period of concerted scientific research on psychedelics, the importance of context was quickly appreciated. The precise origins of the terms ‘set’ and ‘setting’ are difficult to pin down (Zinberg, 1984), but it is clear that they were embraced by the 1960s Harvard academic-turned-psychedelic-popularist Timothy Leary, who used them to refer to the various psychological and environmental influences on a psychedelic drug experience (Leary et al., 1963); ‘set’ being the expectations, assumptions and any other pre-existing psychological factors (including psychopathology) one brings to an experience and ‘setting’ being the environmental context in which it occurs (Hartogsohn, 2016; 2017; Leary et al., 1963). Interestingly, some positive psychological after-effects were reported after the earliest known use of LSD (Hofmann, 1980), despite ‘set’ and ‘setting’ being largely uncontrolled and the acute experience being mostly unpleasant. This apparent paradox, between acutely challenging high-dose psychedelic experiences

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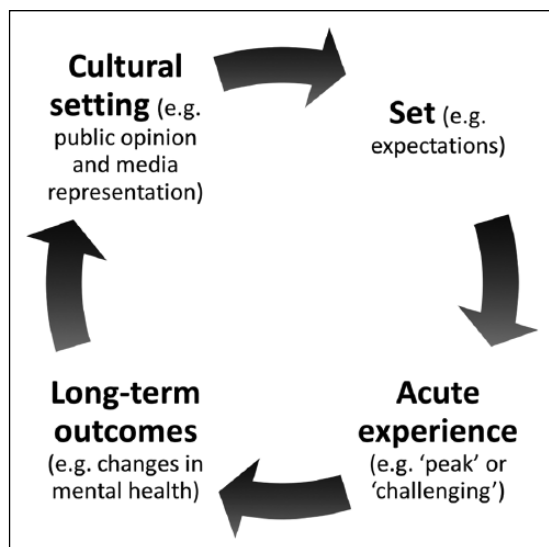


Figure 1. A cultural feedback loop that is hypothesised to contribute to 'set' and thus, the nature of an acute psychedelic experience and its consequent longer-term outcomes. It is proposed that the products of this cyclical process, that is, acute and longer-term responses to psychedelics, feed back into cultural context via media reporting which subsequently affects public opinion, thus influencing the expectations and preconceptions of individuals who intend to take a psychedelic – and so perpetuating the process.

being associated with longer-term psychological benefits, has been highlighted and discussed elsewhere (Carhart-Harris et al., 2016; Carbonaro et al., 2016).

Subsequent therapeutic applications of LSD in the 1950s and 60s did pay special attention to 'set' and 'setting' however – and the associated clinical outcomes were accordingly impressive, with reassuring safety and promising efficacy data (Krebs and Johansen, 2012; Rucker et al., 2016). Crucially, in cases where 'set' and 'setting' were intentionally neglected or even manipulated in a negative way, outcomes were considerably less positive (Albarelli, 2009; Ludwig et al., 1969; Oram, 2014), such as in military experiments with psychedelics in the 1950s and 60s (Albarelli, 2009). It is right to acknowledge that cases of worsened mental health after controlled administrations of psychedelics have been reported (Larsen, 2016; but see Cohen 1960; Studerus et al. 2012 for meta-analyses of prevalence data in controlled research, and Hendricks et al., 2015 and Johansen and Krebs, 2015 for relevant population-level data) and associated legal cases have been fought and won by plaintiffs (but see Erritzoe et al., 2017; Erritzoe and Richards, 2017). In the 1950s and 1960s, rare tragedies linked to psychedelic drug-use (whether fairly or not) were aggressively exploited by conservative media and used to manipulate public opinion and justify policy change in an effective way (Lee and Shlain, 1985). We should be vigilant of this tactic of misinformation and manipulation, lest it be repeated in the context of contemporary psychedelic research.

Only when you sensationalize a subject matter do you get a reform. Without sensationalizing it, you don't... only when the press and television come in do you get action. (Senator

Abraham Rubicon in an official meeting on LSD prohibition, 1966, reported in Lee and Shlain, 1985).

Moreover, if the media and associated public opinion were to turn against psychedelics, as occurred in the mid to late 1960s (Stevens, 1987), it is logical to suppose that this, in turn, would impact on expectations, and subsequently experience, in a self-reinforcing positive feedback loop (Wallace, 1959; Hartogsohn, 2015) (Figure 1). We should be conscious to avoid such a shift in 'cultural set and setting' with regards to psychedelics (Hartogsohn, 2015; Wallace, 1959), particularly if it is initiated by misinformation under a political agenda, as occurred in the late 1960s (Stevens, 1987). Moreover, those considering use of psychedelics without proper recognition of context should be made aware that such bad practice could feed into a negative cultural context loop that could damage the wider therapeutic agenda. Relatedly, it is important to highlight that while opponents of psychedelics can manipulate truth for a particular agenda, so can over-zealous proponents (e.g. see Novak 1998 for a particularly sobering take on the 1950–60s psychedelic research). Heeding lessons from the past, those who see value in the therapeutic potential of psychedelics might be wise to: (a) not push too hard too soon, and (b) be vigilant of their own biases.

Returning to the present day, a number of recent trials have demonstrated promising outcomes with psychologically and environmentally supported psychedelics sessions for psychological distress, mood disorders and addiction (Carhart-Harris and Goodwin, 2017). To our knowledge, all such trials have paid special attention to *context*, providing extensive psychological preparation (often lasting several hours and involving a number of repeat visits before and after the focal psychedelic experiences) and manipulation of the therapeutic environment, for example, with low lighting, carefully selected music playlists, aesthetically pleasing décor and implicit as well as explicit priming.

Moreover, patients enrolled within modern psychedelic trials typically have access to two compassionate mental health professionals. These 'sitters' or 'guides' serve to carefully prepare the patient for their upcoming experience, support them during it, and help them integrate its content and meaning afterwards (Johnson et al., 2008; Richards, 2015). Such intensive support is unusual in the context of conventional mental health-care services, and despite its questionable feasibility in terms of time and associated costs, it has been the norm in modern psychedelic trials. In a similar way to how Good Clinical Practice training ensures a standard of practice in clinical research, specific training for psychedelic therapy may need to be developed, standardised and licensed if patient safety is to be maintained. With large clinical trials of psilocybin for treatment-resistant depression planned in the near future (Jack, 2017), it is reassuring that such matters are currently being addressed.

We share the view of others (Johnson et al., 2008; Richards, 2015) that the experiential component of psychedelics necessitates and facilitates the development of a strong therapeutic bond between the patient and his/her guides. Moreover, although this way of working might initially challenge overstretched healthcare systems, it could also afford an opportunity to resurrect the 'care' element that some service-users have found lacking in current mental

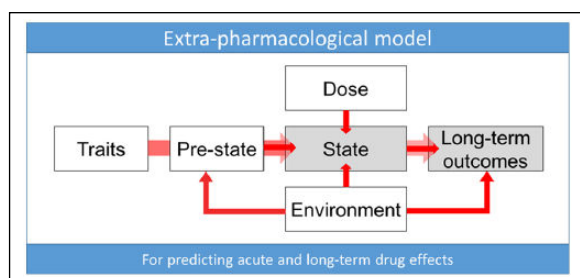


Figure 2. Extra-pharmacological model of drug action that takes into account salient contextual factors – see (Carhart-Harris and Nutt, 2017) for discussion. This model is complementary to the cultural feedback loop model shown in Figure 1. Note: the term ‘pre-state’ is interchangeable with ‘set’.

healthcare practice (Watts, 2017; Bentall, 2009). Therapeutic alliance is already known to be a major predictor of response in mental healthcare (Kazdin, 2007) and if the present thesis is correct, its influence is likely to be greater still in the context of psychedelics (see Carhart-Harris and Nutt, 2017).

Taking stock of these things, it is reasonable to suspect that ‘favourable context’ has contributed significantly to the favourable outcomes that have been reported in recent clinical trials with psychedelics. Indirect support for this may be found in the not inconsiderable (before-versus-after treatment) effects sizes observed in control conditions in recent double-blind randomised control trials of psilocybin for end-of-life distress, for example (Griffiths et al., 2016). It seems unlikely that such effects can be attributed entirely to conventional ‘positive expectancy’ – the basis of the standard placebo effect (Kirsch, 2013) – although see Demyttenaere (2016) and Goodwin (2016) – nor to a low-level pharmacological effect if presumed-inactive doses of the experimental drug are used as the control (e.g. 1 mg/70 kg for 75% of the patients in Griffiths et al. 2016). Most likely in our view, is a favourable-context effect mediated by positive expectancy and exceptional care. This said, if a sufficient active dose of a psychedelic is given, it seems reasonable to suspect that contextual influences would be amplified by the plasticity-promoting effects of serotonin 2A receptor signalling (see Carhart-Harris and Nutt, 2017).

Comprehensive approaches to drug action, that properly acknowledge context, have been gaining traction in psychopharmacology in recent years, as evidenced by seminal gene $\times$ environment (Caspi et al., 2010), drug $\times$ cognition (Harmer and Cowen, 2013), and drug $\times$ environment (Alboni et al., 2017) interaction work. The central argument of the present paper is that at least the same degree of emphasis needs to be placed on extra-pharmacological factors in relation to psychedelics – Figure 2 (see Carhart-Harris and Nutt, 2017). Indeed, in line with recent hypotheses (Branchi, 2011; Carhart-Harris and Nutt, 2017) and findings (Chiarotti et al., 2017), it is proposed that the pro-plasticity effects of serotonin (Branchi, 2011) – and serotonin 2A receptor agonism particularly (Carhart-Harris and Nutt, 2017; Jokela et al., 2007; Jokela et al., 2007a, Jokela et al., 2007b) – renders the psychedelic experience exceptionally sensitive to context. Insufficient appreciation of this principle may lead to risky and potentially harmful applications of psychedelics – which could jeopardise the healthy progress of psychedelic research – as well as the mental health of anyone who misuses these drugs (Oram, 2014).

Remarkably, despite its widespread adoption among psychedelic researchers, few controlled studies have ever been performed to test the assumed relationship between psychedelics and context (although see Ludwig et al., 1969). In terms of our own research, the closest we have come to testing this has been to investigate the influence of music (Kaelen et al., 2015; Kaelen, 2018), positive autobiographical memory scripts (Carhart-Harris et al., 2012) and creative imagery/suggestibility on the psychedelic experience (Carhart-Harris et al., 2015), and in all cases we have found an enhanced influence in the drug condition versus placebo. Moreover, we have also found that patients’ relationship to the music they listen to during psilocybin therapy sessions is predictive of the quality of their experience, which in turn is predictive of long-term therapeutic outcomes (Kaelen et al., 2017).

It is logical to infer from such findings that psychedelics’ specific pharmacology works synergistically with context, creating a certain kind of experience that is conducive to particular outcomes (Carhart-Harris and Nutt, 2017; Garcia-Romeu et al., 2014; Griffiths et al., 2016; MacLean et al., 2011; Roseman et al., 2017; Ross et al., 2016). Increased serotonin 2A receptor signalling mediating cortical plasticity and an associated sensitivity to internal (i.e. endogenous processes and pre-existing mental context) and external influence (i.e. the environment), is proposed to be the key underlying mechanism (Carhart-Harris and Nutt, 2017). It is interesting to consider whether the impact of a given contextual factor is dependent on the level at which it captures and resonates with an individual’s underlying emotional and cognitive state (Kaelen et al., 2017). Relatedly, we have often observed that participants are relatively insensitive to conventional task-based stimuli under psychedelics, as the relevant stimuli fail to engage their attention and/or interest (see Timmermann et al., 2017 for a relevant discussion).

Looking to the future, it seems vital that new studies be conducted to test the hypothesised primacy of context in shaping the nature of a psychedelic experience, so as to mitigate risks and foster the development of optimal treatment approaches. It is arguably already well established that the quality of an acute psychedelic experience is predictive of its longer-term effects (Roseman et al., 2017), and on this basis, the quest for a non-psychedelic but still therapeutically effective serotonin 2A receptor agonist may eventually, in our view, hit a dead end. Indeed, a similar principle may apply in the context of ketamine for depression research and the search for non-psychoactive NMDA receptor modulators with therapeutic efficacy equivalent to that of ketamine (Luckenbaugh et al., 2014; Sos et al., 2013). In our view, a proper acknowledgement of the importance of context and experience would represent a positive paradigm shift in pharmacological care in psychiatry.

Previous work has shown that the dose of a psychedelic is a reliable predictor of the nature of the subsequent psychological response (Griffiths et al., 2011; Nour et al., 2016; Studerus et al., 2012). There is also evidence that spatially confined neuroimaging settings can increase the likelihood of challenging experiences with psychedelics (Studerus et al., 2012). This is something we have witnessed on at least two occasions (in approximately 100 psychedelic scan sessions) with magnetic resonance imaging and magnetoencephalography separately – although in retrospect, both cases of transient anxiety may have been as much to do with negative ‘set’ as the

imaging setting itself. Where feasible, future psychedelic imaging studies may consider improvements to the imaging setting through the inclusion of music, the recruitment of scanner-experienced participants and opportunities for better pre-session briefing and post-session psychological integration, as is default in most (if not all) recent and current clinical trials.

Other than the aforementioned dose-response study (Griffiths et al. 2011) and retrospective analyses (e.g. Studerus et al. 2012), controlled studies designed to isolate and test key contextual variables assumed to influence the quality of a psychedelic experience have not yet been carried out (but see Ludwig et al. 1969). It is likely that this is due to the practical and ethical challenges raised by providing a sub-optimal (let-alone negative or adverse) context for a full-dose psychedelic experience (Oram, 2014). One way to resolve this matter may be to design a study involving low doses of a psychedelic, in which the provision of a sub-optimal context is feasible.

As touched on briefly above, there has been an emerging interest in so-called psychedelic ‘microdosing’ in recent years, a practice of ingesting sub-threshold-to-threshold psychoactive doses of a psychedelic 2–3 times per week for a given number of weeks while the ‘user’ goes about their normal life (Fadiman, 2017; Waldman, 2017). While there is as yet no published peer-reviewed scientific evidence to support the safety and efficacy of this practice, enthusiastic claims have been made about its impact on mood, well-being and creative thinking (Fadiman, 2017; Waldman, 2017).

One alleged merit of microdosing (over ‘full-dosing’) is that context may be less influential. While this assumption may turn out to be reliable, there are valid pharmacological reasons to believe that context may still be important, even with regards to microdosing (Carhart-Harris and Nutt, 2017). A controlled study designed to test this would add value, not just in terms of providing a timely examination of the current claims about microdosing, but also by testing the potentially important association between serotonin 2A receptor signalling and sensitivity to context (Carhart-Harris and Nutt, 2017). Back-translation involving comparable environmental (Alboni et al., 2017) and more selective pharmacological manipulations (Ashby et al., 1994) in non-human animals could serve to sharpen inferences on any positive findings from human research.

The number of factors impinging on a psychedelic experience may be vast. Thus, endeavouring to test them all independently and in combination is a huge challenge. Initially, we propose testing those elements about which we hold particularly strong prior hypotheses (e.g., that music and psychotherapy are critical components of the treatment model) but there may also be another, supplementary approach.

Psychedelics are an anomaly among drugs of ‘potential misuse’ (Hendricks et al., 2015), not least because those who wish to have a psychedelic experience often plan ahead for it, sometimes travelling vast distances to specific retreat centres to receive a given psychedelic in a particular context (Winkelman, 2005). Exploiting this phenomenon, we recently set up a web-based survey system (psychedelicsurvey.com) in which individuals who plan to take a psychedelic can enter the date of their planned experience and then receive specific surveys at strategic time points: (a) 1 week before, (b) 1 day before, (c) 1 day after, and then (d) 2 weeks after the focal experience. In this way we sought to test the *process of change* related to a psychedelic experience,

assessing a large number of potentially salient factors and their relevant contributions to acute and longer-term outcomes in a large sample.

Preliminary results from this project can be seen in Figure 3 (see a forthcoming publication for a more complete account of this study’s methods and results). In model 1, it can be seen that: (a) feeling ready to ‘surrender’ to the experience, (b) having a *clear intention* for it, (c) having the experience in a *therapeutic setting*, and (d) taking a higher *dose*, are all predictive of having a certain kind of psychedelic experience which we label ‘peak’ – an intentionally secular term inspired by Abraham Maslow’s work (Maslow, 1976) – that can effectively be viewed as a synonymous with the concept of a ‘mystical’ experience (Griffiths et al., 2006; Richards, 2015). Conversely, model 2 reveals that the same factors – plus being in the company of well-trusted individuals – protect against a ‘challenging’ psychological experience (what some might refer to, perhaps too crudely, as a ‘bad trip’). Consistent with previous work (Griffiths et al., 2016; Roseman et al., 2017; Ross et al., 2016), we found that having a peak experience is predictive of improvements in psychological well-being 2 weeks after the experience (model 1), whereas having a challenging experience predicts a deflation of this effect on well-being (model 2). While higher doses do not strongly predict challenging experience in this sample, it seems sensible to assume that biases exist within it (such as extensive prior experience with and positive attitudes towards psychedelics), and other studies have suggested that exceeding an optimal dose for peak experiences (e.g., approximately 25–30 mg psilocybin) may risk inflating challenging aspects without adding any appreciable gain in terms of therapeutic benefit (Griffiths et al. 2011).

Briefly, based on additional measures included in this project, we are presently working towards resolving putative inconsistencies between our data and previous findings. More specifically, whereas we saw a trend relationship between challenging experience under a psychedelic and less of an increase in psychological well-being 2 weeks later, others have found evidence that challenging experiences can be therapeutically beneficial (Barrett et al., 2016; Carbonaro et al., 2016). Potentially resolving this discrepancy, we believe that challenging experiences can indeed be therapeutically beneficial but only if personal insight and/or an emotional catharsis follows the relevant experience(s) of psychological struggle. To test this assumption, we are presently developing an ‘emotional breakthrough’ measure, which was applied in the presently described survey project to good effect. It is also worth noting that previous studies supporting the therapeutic potential of challenging experiences required that participants focus on their most challenging psychedelic experience. Moreover, the ‘long-term’ outcomes shown in Figure 4 are based on reports 2 weeks post experience; it seems reasonable to suppose that therapeutically valuable processes of psychological integration can take longer than 2 weeks to resolve after a particularly challenging psychedelic experience (Aixala, 2017).

In summary, this article has sought to highlight the essential importance of *context* in determining the quality of a psychedelic experience and its longer-term outcomes. It is proposed that neglect of this essential component of the psychedelic treatment model may account for the rare cases of psychological harm that have been reported in association with psychedelic use (Larsen, 2016) which have (disproportionately) contributed to their historical negative stigma (Lee and Shlain, 1992). The more

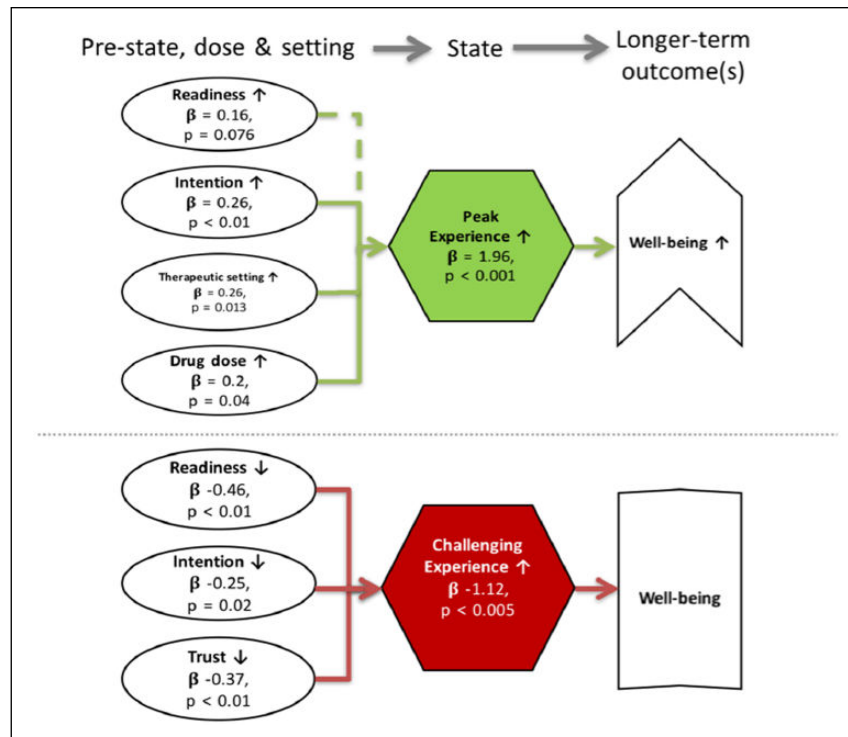


Figure 3. Predicting a trip: Two models based on data derived from web-based survey in 266 participants who completed surveys at four key time points: (a) 1 week before; (b) 1 day before; (c) 1 day after; and (d) 2 weeks after a specific psychedelic experience. The top model shows factors predicting a 'peak' or 'mystical-type' experience under a psychedelic, which subsequently predicts improvements in psychological well-being 2 weeks later. The bottom model shows factors which (if lacking) predict a challenging psychological experience under a psychedelic, which subsequently predicts a reduced increase in psychological well-being 2 weeks later. Arrows with full lines represent significant relationships between factors and broken lines are used for trend-level relationships. *Readiness* contains four items such as 'I feel ready to surrender to whatever will be' and 'I feel open to the upcoming experience'; *intention* contains two items, namely: 'I have a clear intention for the upcoming experience' and 'I have strong expectations for the upcoming experience'; *trust* contains two items, namely: 'I have a good feeling about my relationship with the group/people who will be with me during my experience' and 'I have a good relationship with the main person/people who will look after me during the upcoming experience'. This study will be reported more fully in forthcoming publications.

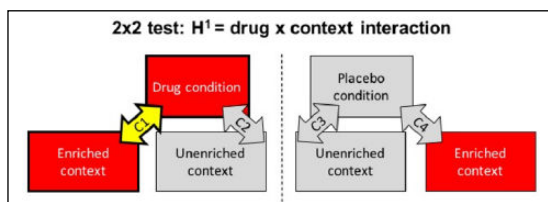


Figure 4. Proposed 2x2 model to test the hypothesised positive interaction between a psychedelic and an enriched context (condition 1, C1). As throughout this paper, the term 'context' is used generically but could refer more specifically to either *environmental* or *psychological* enrichment versus an un-enriched or even adverse context (Branchi, 2011). For example, controlled studies could be designed to test: music versus no music or low lighting versus standard bright lighting (*environmental context*); or psychotherapy versus no-psychotherapy, or priming versus no-priming (*psychological context*). We propose that the implementation of such designs would be safest and most feasible if the dose of the relevant psychedelic is kept *low*, so as to mitigate potential risks associated with condition 2 (C2). Repeat (low) dosing could be implemented as per a classic microdosing model (<https://thethirdwave.com>; Fadiman, 2017; Waldman, 2017). With regards cultural context (see Figure 1.), one might even consider a cross-cultural study in which key outcomes are compared in a culture where psychedelic use is legal and celebrated (e.g. in Amazonian regions) versus one in which it is illegal and stigmatised (e.g. in Western countries).

optimistic and progressive counterpart to this, however, is that a careful and honest management of context may serve to minimise harm and maximise the considerable therapeutic potential of psychedelics (Carhart-Harris and Goodwin, 2017; Carhart-Harris and Nutt, 2017), yielding a powerful treatment model with a compelling neuropsychological action that could potentially benefit a broad cross-section of the populace (Carhart-Harris et al., 2018; Carhart-Harris and Nutt, 2017).

The future success of psychedelic medicine will depend much on how scientists, clinicians, investors and policy makers receive this complex, composite and paradigm-challenging treatment model. Our view is that greater utilisation of drug × context synergies may form part of an important paradigm shift in psychiatric care. Another view, however, is that factoring in context is problematic, since it (over)complicates traditional pharmacological models by adding extra psychological variability and practical and financial burdens related to delivery of care and associated costs. In response to this, it could be fairly argued that the notion that the efficacy of traditional pharmacotherapies is exempt from context is flawed (Alboni et al., 2017; Branchi, 2011) and that the psychedelic treatment model, while costlier in terms of delivery, may actually be cost-saving in terms of therapeutic action (Carhart-Harris et al., 2018; Watts et al., 2017) due to the potential long-term duration of clinical response after just a small number of treatment sessions (Carhart-Harris and Goodwin, 2017).

For the sake of science and healthcare over politics, we must hope that the future be allowed to properly test and tell.

Authors' contributions

This article was written by RCH. All authors read, commented on and approved the final manuscript.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: RCH is supported by the Alex Mosley Charitable Trust and has served as an advisor for Compass Pathways. We are grateful to Kenneth Jonck and Nicolai Lassen for their work in relation to Psychedelicsurvey.com, as well as to those who completed the survey.

Note

1. By 'psychedelics', we refer to the classic psychedelics such as LSD, psilocybin/psilocin and dimethyltryptamine/ayahuasca, pharmacological definable by serotonin 2A receptor agonism.

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