A Role for Enhanced Functions of Sleep in Psychedelic Therapy?

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Keywords: rat models; psilocybin; memory consolidation; psychedelic assisted therapy; altered states of consciousness; sleep

ABSTRACT

After a hiatus of several decades there has been a resurgence of studies into the therapeutic potential of serotonergic psychedelics. When administered in controlled settings, they have been reported to induce a wide variety of long-lasting positive psychological changes. However, the mechanisms by which psychedelics impart these long-lasting benefits remain poorly understood. Here we highlight one possibility that has remained underexplored: a beneficial interaction with the self-optimizing functions of sleep.

BACKGROUND

There is a resurgence of studies into the therapeutic potential of serotonergic psychedelics, especially of N, N-diethyllysergamide (LSD) and psilocybin (Kupferschmidt, 2014). Although these substances acutely alter perception, mood, and cognition, they are generally considered physiologically and psychologically safe and, unlike many other mind-altering drugs, they do not lead to dependence (van Amsterdam et al., 2011; Nichols, 2016). When administered in controlled settings, they have been reported to induce long-lasting positive changes: improvements in wellbeing and mood in healthy subjects and in patients suffering from severe depression and anxiety, attenuation of addictions, and reduction in unwanted behavioral patterns (for reviews, see Dos Santos et al., 2016; Garcia-Romeu et al., 2016; Carhart-Harris and Goodwin, 2017).

However, the mechanisms by which psychedelics impart these long-lasting benefits remain poorly understood, and more theoretical work is urgently required in order to guide future empirical research in the most fruitful directions. Here we would like to highlight one

possibility that has remained underexplored in the current literature: a beneficial interaction with the functions of sleep. In the next section we briefly review the most prominent theoretical approaches and assess how they relate to sleep.

THEORIES OF PSYCHEDELIC THERAPY

Vollenweider and Kometer (2010) proposed that the antidepressant effects of psilocybin are based on the modulation of the neural circuits implicated in mood and affective disorders, and that the reduction in symptoms outlasts the acute effects due to glutamate-dependent neuroplastic adaptation. However, it is not clear how this proposal could account for the full range of benefits of psychedelic therapy, such as smoking cessation. It also does not incorporate recent findings of global changes in brain activity during the acute state, which consistently point toward an essential role of more unconstrained functioning, as measured by heightened entropy, signal diversity, or reduced top-down control (Alonso et al., 2015; Schartner et al., 2017). Neither does this hypothesis consider a role for sleep.

Carhart-Harris and colleagues (2014) developed a more general hypothesis, the Entropic Brain Hypothesis (EBH), based on these recent findings. The EBH proposes that neural entropy is suppressed in normal waking consciousness because this enhances focused problem solving. Accordingly, the EBH identifies a potential problem: if the brain decreases its entropy by too much its functioning can become overly constrained. The brain's entrapment in a rigid state is said to be a factor underlying many psychopathologies, for example depression, obsessive-compulsive disorder, and addictions. It is hypothesized that psychedelics are beneficial in these cases because the acute increase in entropy is partially retained after the patient returns to the normal state (Carhart-Harris et al., 2016). It is not clear what mechanism is supposed to retain the increased levels of entropy, but the EBH could perhaps appeal to the modulation of neuroplasticity discussed by Vollenweider and Kometer (2010). The EBH explicitly acknowledges that the psychedelic state and the REM sleep state have similar system-level mechanics and styles of cognition (Carhart-Harris et al. 2014), but it does not go so far as to consider their possible interaction.

The EBH can be distinguished from a longer tradition in the study of altered states of consciousness, which accounts for their therapeutic benefits in terms of increased order, for example in terms of enhanced neural, psychological, and social integration (Freeman, 1999; Winkelman, 2010). At first sight this alternative may appear to be in conflict with the disordered nature of the acute state. However, temporary increases in disorder can drive long-term increases in order, an insight long employed in cybernetics and machine learning techniques such as simulated annealing. The key idea of this alternative theoretical approach is that the interruption induced by the acute state leads to a reorganization of constraints such that post-acute state neural activity becomes more integrated and optimally coordinated. We refer to this perspective as the Self-Optimization Hypothesis (SOH). As we will now show, this way of understanding the efficacy of psychedelic therapy naturally leads us to consider a possible interaction with sleep.

We can make sense of the SOH in a formal manner in terms of a particular model of self-optimization in complex adaptive systems: Watson and colleagues (2011) demonstrated that combining *(a) neuroplasticity* and *(b) relaxations of constraints on neural activity*,

which was implemented by intermittently setting activity to random states, can spontaneously lead to structural reorganization of the network such that it facilitates more optimal large-scale neural coordination. The central insight is that the repeated temporary removal or alteration of normal functional constraints, followed by re-convergence to normal functioning, allows the neural network to explore and learn the layout of its own state space. These interruptions have to be sufficiently large in order to be effective; if the changes of neural activity are too small the network will not escape the basin of attraction of its current optima and will therefore fail to learn other possible configurations.

Woodward, Froese, and Ikegami (2015) argued that this self-optimization model helps us to understand how benefits could be imparted by the psychedelic state and by altered states more generally, including the sleep-wake cycle, given that sleep also temporarily allows the brain to escape the constraints of its normal functioning. We can therefore envision two non-exclusive scenarios: (1) the psychedelic state permits the brain to explore and learn a wider range of its state space, which in itself can improve the brain's capacity for large-scale neural coordination, and (2) psychedelics interact with the sleep state so as to potentiate its effect of temporarily shifting the brain into non-ordinary regions of its state space, which would be particularly useful in circumstances when, for whichever reason, the interruptions provided by sleep are not sufficient for effective self-optimization.

The SOH is starting to be confirmed by the first studies of post-acute psychedelic state brain activity, which find significant increases in functional connectivity compared to the pre-acute state (Carhart-Harris et al., 2017; Sampedro et al., 2017). We expect the number of studies comparing post- and pre-acute state brain activity to increase, allowing a more precise comparison between the EBH and SOH. Will the long-term post-acute state neural entropy turn out to be higher compared to the pre-acute state, as per EBH, or lower, as per SOH? This is an important open question that is close to being resolved empirically. At the same time the hypothesized relationship between sleep and the psychedelic state, especially in the context of understanding the basis of its long-term benefits, also deserves more attention in future research. Currently their interaction is still poorly understood.

SLEEP, PSYCHEDELICS, AND THERAPY

The many neurophysiological and experiential similarities between the psychedelic state and the dreaming or REM stage have long been highlighted (Hobson, 2001; Carhart-Harris and Nutt, 2014). The desynchronization of the occipital alpha rhythm with eyes closed, resulting in EEG patterns similar to REM sleep, is one of the most consistent findings across recent studies with psychedelics in humans (Riba et al., 2004; Muthukumaraswamy et al., 2013; Kometer et al., 2015). Furthermore, suppression of the activity of the serotonergic system, typically induced by tryptamine psychedelics via 5-HT1A agonism (Nichols, 2016), is in line with the decreased monoamine tone necessary for REM phases of sleep (Rasch and Born, 2013).

However, there are also important differences. First, the psychedelic state contrasts strongly with dreamless or NREM sleep (Tagliazucchi et al., 2016; Schartner et al., 2017). Second, in contrast with REM sleep, the dreaming-like experiences of the psychedelic state occur during full wakefulness. Animal studies with LSD and tryptamine (Kay and Martin, 1978),

mescaline (Colasanti and Khazan, 1975), and DOI (Monti and Jantos, 2006) consistently describe a significant increase in wakefulness and an inhibition/reduction of REM and slow-wave NREM sleep. Most human subjects exposed to LSD also report difficulties sleeping afterwards, but this effect has not been investigated. To our knowledge only one human study explored sleep in the night after the exposure to a serotonergic psychedelic, the brew Ayahusaca[1], and found decreased REM sleep and enhanced power of slow-wave NREM sleep (Barbanoj et al., 2008). However, this effect might be related to the *β*-carboline monoamine oxidase-inhibitors (MAOIs) contained in the brew, since MAOIs can completely eliminate REM phases of sleep and dreaming (Siegel, 2001). In sum, it seems reasonable to assume that psychedelics affect sleep architecture, but there is currently a lack of data to specify the nature of this interaction.

Both the EBH and SOH can accommodate a possible role for enhanced functions of sleep in psychedelic therapy. Yet their different stances toward the role of entropy lead them to propose different mechanisms. Sleep has the effect of counteracting the tendency of neural activity to shift from a critical to a supercritical state during prolonged wakefulness, thereby restoring it to the more optimal critical state (Meisel et al., 2013). According to the EBH the general problem underlying many mental disorders is that the brain overcompensates the tendency to increasing entropy and is thus forced into a subcritical state, which overly constrains its cognitive functioning. Thus, the EBH could predict that psychedelics are beneficial because they interact with sleep mainly in an inhibitory manner, thereby preventing it from reducing the entropy of the waking state by too much. In contrast, the SOH predicts the opposite, namely a positive interaction such that sleep's function of shifting neural activity from a supercritical to a critical state is enhanced. The evidence is currently ambiguous: studies showing effects of increased wakefulness appear to support the prediction of the EBH, whereas studies showing effects of enhanced power of NREM sleep suggest that the SOH could be on the right track instead.

Further research is evidently needed. We suggest that one practical way of testing these hypotheses is in terms of their divergent predictions regarding the interaction between psychedelics and impaired sleep: the EBH would predict that administering psychedelics worsens the effects of sleep deprivation, given that it would further disrupt and inhibit sleep. The SOH, on the other hand, would predict that psychedelics would counteract the deleterious effects of sleep deprivation, given that it would complement and/or enhance the functions of sleep, following the two scenarios we had envisioned above. In the next section we present evidence that supports the SOH's prediction.

PSILOCIN, SLEEP, AND MEMORY

So far a role for enhanced functions of sleep in psychedelic therapy has not been explicitly investigated. Nevertheless, a behavioral study by Rambousek, Palenicek, Vales, and

[1] Ayahuasca is a traditional hallucinogenic brew containing a mixture based on psychedelic tryptamine N,N-dimethyltryptamine (DMT) and monoaminooxidase inhibitors harmine, tetrahdyroharmine and harmaline

[2] Psilocin (4-hydroxy-N,N-dimethyltryptamine) is the active metabolite of psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine). They act as agonists at serotonin receptors, mainly 5-HT2A/C and 5-HT1A subtypes (for a review, see Tylš et al., 2014).

Stuchlik (2014) investigated the effect of psilocin[2] on spatial memory in rats, including on memory consolidation during the "lights on" condition of their circadian cycle (therefore during their natural sleep period). Even though the authors followed the standard approach of ignoring possible interactions between psychedelics and sleep, their study fortunately provides us with a suitable starting point to test the competing predictions of the EBH and SOH regarding impaired sleep.

They used the Morris water maze paradigm (Figure 1). A rat was placed in a large circular pool of water and required to swim until it finds a hidden platform on which to rest. If a rat fails to locate the platform within 60 seconds, the trial is terminated and the experimenter guides the rat to the platform to nevertheless permit the formation of spatial memory. There are no local cues inside the pool, so during the first trial it can only be found by chance. In subsequent trials its location can be identified faster based on spatial memory, and so reducing latency can be used as an indicator of spatial memory consolidation.

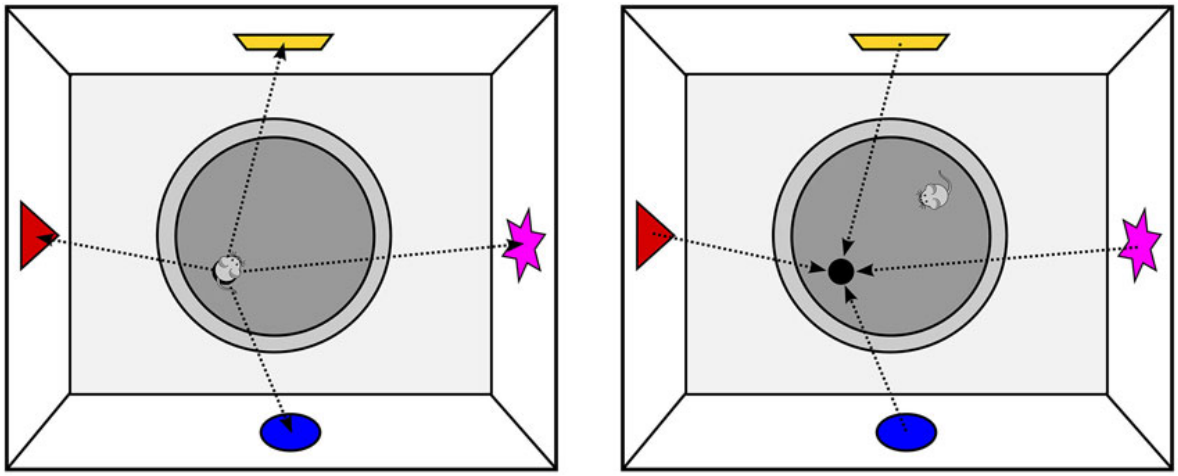

Figure 1. Illustration of the Morris water maze task. A small animal, typically a rat, is put to swim in a circular pool devoid of local cues but surrounded by visual landmarks in the room. *Left:* once an animal has chanced upon the submerged platform upon which it can rest, it can memorize the spatial relationship between the platform and extra-maze cues. *Right:* in a subsequent trial the animal can relocate the hidden platform faster based on spatial memory. Figure taken from Wolbers and Wiener (2014) under the Creative Commons license.

Rambousek et al. tested 3 groups (one control, two test groups), consisting of 8 rats each, for 16 trial swims on Day 1, followed by psilocin injection immediately *after* the last swim at doses of 1 or 4 mg/kg for the low-dose and high-dose groups, respectively. On Day 2 the rats were retested on the same maze configuration for another 8 trials without injections. Surprisingly, the authors remarked that there was slightly better performance on Day 2, but did not pursue this finding further. We were motivated by this remark to do a systematic re-analysis of their data and to explicitly consider a possible interaction with sleep.

[2] Psilocin (4-hydroxy-N,N-dimethyltryptamine) is the active metabolite of psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine). They act as agonists at serotonin receptors, mainly 5-HT2A/C and 5-HT1A subtypes (for a review, see Tylš et al., 2014).

RE-ANALYSIS AND RESULTS

We specified a hierarchical model (trials nested within individuals), allowing for a *linear learning effect as a function of trial number*, separately for the two days[3]. Furthermore, parameters (separately for Day 1 and Day 2) are included to account for individual differences in the intercepts and slopes; *only on the second day these differences are associated with the experimental condition* (since psilocin was administrated after the 16th trial on the first day).[4] *Time values of 60 seconds are treated as censored data*. We fitted the model in a *Bayesian framework* using Markov chain Monte Carlo simulation (see, e.g., Gelman et al., 2004). All details of the statistical model can be found in the online Supplementary Material.

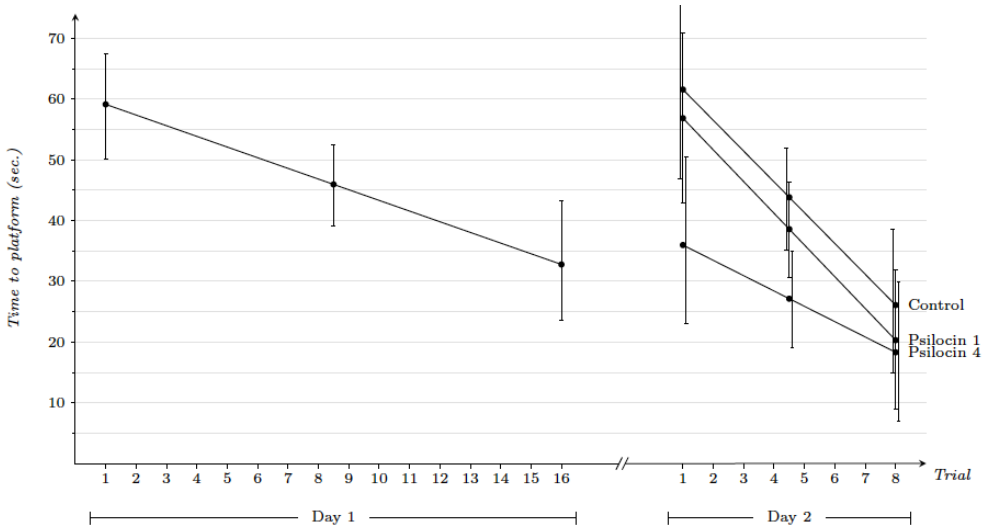

Figure 2. Latencies of rats to reach a hidden platform in the Morris water maze task as a function of trials, days, and conditions as estimated by the statistical model used for reanalysis of the data obtained by Rambousek et al. (2014) (see main text and Supplementary Material for details). The midpoints of the lines represent mean latencies across trials of the given day. Bars represent the 95% Bayesian credibility interval associated with the estimate at the given point.

We highlight the following outcomes:

(a) As shown in Figure 2, all the slopes are negative, which means that on Day 1 (overall) as well as on Day 2 (for each condition) there is a learning effect. There is no evidence that the learning effects are different.

(b) The mean time to reach the platform (see the midpoint of each line in Figure 1) is lower on Day 2 than on Day 1 for the rats of both the low-dose (posterior *p*-value = .03)

[3] Italics in this paragraph highlight differences between our reanalysis and the original analysis.
[4] In order to check the validity of the experimental procedure, we performed a statistical test comparing a model which includes the restriction of equal overall regression lines for the three experimental groups on Day 1 versus the unrestricted model, which allows for different regression lines. This test computes a Bayes Factor (Kass and Raftery, 1995) with a value of 6.5, which indicates that the evidence provided by the data favors the assumption of equal regression lines.

and the high-dose group (posterior *p*-value < .001). Furthermore, comparisons for Day 2 reveal that the mean latency in the high-dose group is lower than in the low-dose group (posterior *p*-value < .01) as well as in the control group (posterior *p*-value < .01). A secondary analysis, based on an alternative model that restricted the effect on mean time of the second day to be a linear function of dose, showed a decrease in latency of 4.04 seconds per 1 mg/kg psilocin (95%-Bayesian credibility interval = [1.60, 6.33]).

(c) The differences among the three conditions on Day 2 with respect to mean latency are principally due to the first trials; gradually, these differences become smaller and at the end there is no longer any evidence of a performance difference.

In summary, when averaging across trials per day, the control group exhibited no difference when comparing Day 1 and Day 2, which is consistent with other studies (e.g. Rahman et al., 2013), although statistically significant reductions in control group latency have been reported in other studies (e.g. Smith and Rose, 1996). In comparison, there was a dose-dependent reduction in latency on Day 2, which could be interpreted as psilocin-enhanced spatial memory consolidation. This would complement evidence that post-training stimulation of serotonin 5-HT_{2A} receptors enhances object memory consolidation (Zhang and Stackman Jr., 2015).

Nevertheless, trial-by-trial analysis suggests a more nuanced explanation of this positive effect because the control group performed significantly worse during Trial 1 on Day 2 when compared to the last trial of Day 1. In fact, its performance during Trial 1 on Day 2 is no different from Trial 1 of Day 1. This loss of spatial memory is likely a result of performing the trials during the phase when rats normally sleep. Indeed, it is known that a significant impairment of performance in Trial 1 on Day 2, without any impairment of working memory, can be experimentally induced via REM sleep deprivation (Youngblood et al., 1997). Thus, while we still cannot say whether psilocin can *enhance* sleep's function of memory consolidation, due to the lack of a condition without sleep impairment, at least it appears to be able to *compensate the loss* of this function in a dose-dependent manner. This compensation, which has previously gone unrecognized in the literature, is in line with the positive interaction between psychedelics and sleep predicted by the SOH.

FINAL REMARKS

We suggest that one way in which psychedelics may impart their long-term benefits is by interacting with sleep. This possibility has been ignored in the current literature, but it is a fitting target for further investigation. Sleep is also an altered state associated with long-term benefits based on neural reorganization and optimization, including improvements in mood (Landmann et al., 2015; Ravassard et al., 2015). As cited above, several published findings indicate a complex interaction between psychedelics and different stages of sleep, and our re-analysis has for the first time revealed evidence that there can be a beneficial interaction with the functions of sleep under some circumstances. Moreover, our finding of dose-dependent compensation of impaired spatial memory consolidation, if substantiated by more systematic follow-up studies, would suggest that psilocin may have unsuspected applications in the treatment of age-related or pathological memory loss. Further theoretical

and experimental research is therefore warranted to determine the extent and nature of the interaction between psychedelics and sleep.

AUTHOR CONTRIBUTIONS

T.F. hypothesized that a re-analysis of Rambousek et al.'s (2014) data would reveal evidence of enhanced sleep-dependent learning and wrote the initial draft. I.L. performed the statistical re-analysis. T.P. participated in the original study by Rambousek et al. and provided expertise on the effects of psychedelics on sleep and on recent research with psychedelics. All authors contributed to shaping the final manuscript.

FUNDING

T.F. was supported by UNAM-DGAPA-PAPIIT project IA104717 and CONACyT project 221341. T.P. was supported by project Nr. LO1611 from MEYS CR under the NPU I program, MICR VI20172020056, and PROGRES Q35.

ACKNOWLEDGEMENTS

Lukas Rambousek performed the original behavioral experiments under the supervision of Ales Stuchlik. We are grateful to Lukas for sharing his experimental data with us. T.F. thanks Dobromir Dotov for performing a first reanalysis of that data.

Data available on request.

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