Effects of varied doses of psilocybin on time interval reproduction in human subjects

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Abstract

Action of a hallucinogenic substance, psilocybin, on internal time representation was investigated in two double-blind, placebo-controlled studies: Experiment 1 with 12 subjects and graded doses, and Experiment 2 with 9 subjects and a very low dose. The task consisted in repeated reproductions of time intervals in the range from 1.5 to 5 s. The effects were assessed by parameter \( \kappa \) of the ‘dual klepsydra’ model of internal time representation, fitted to individual response data and intra-individually normalized with respect to initial values. The estimates \( \hat{\kappa} \) were in the same order of magnitude as in earlier studies. In both experiments, \( \kappa \) was significantly increased by psilocybin at 90 min from the drug intake, indicating a higher loss rate of the internal duration representation. These findings are tentatively linked to qualitative alterations of subjective time in altered states of consciousness.

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Awareness of temporal order of events and the ability to discriminate temporal durations are typical for the normal, wakeful conscious state, whereas alterations of subjective time experience are often observed in so-called ‘altered states of consciousness’ (ASC) [11,8,4,18]. Therefore, artificially induced ASCs provide good experimental models for testing concepts and hypotheses concerning ‘subjective time’ and, particularly, models of internal time representation.

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) induces psychosis-like states, most likely by agonist action at serotonin 5-HT\(_{2A/1A}\) receptors [19]. Alterations of time experience in psilocybin-induced states were subjectively reported [6], and recently objectively measured [28]. Psilocybin significantly shortened subjects’ reproduction of temporal intervals longer than 2.5 s, impaired their ability to synchronize to inter-beat intervals longer than 2 s, and slowed down their preferred tapping rate. Working-memory deficits and subjective changes in conscious state, including disturbances in subjective time sense, were also observed. These effects are in line with the evidence for psilocybin’s action via serotonergic modulations of prefrontal cortex activity [2], and with the important role of prefrontal cortex in time perception and timing behavior [14,9,29].

The aforementioned results concerning the effects of psilocybin on duration reproduction [28] were based on the evaluation of reproduction effects undertaken separately for each stimulus duration. An alternative strategy is to study the subject’s response function across the whole range of stimulus durations, using a suitable parametric model, and assessing differential effects in terms of model parameters rather than response times. All subject’s data are thus taken into account at once; degrees of freedom are determined solely by the model’s parameterization, not by a particular experimental design.

The following analyses rely on the ‘dual klepsydra’ model (DKM) of duration reproduction [20,23]. The DKM is based on an accumulation principle, similarly to the standard pacemaker–counter model, also called ‘internal clock’ model (ICM) [1], but there are important differences. The ICM emulates a digital electronic stop-watch, whereas the DKM is rather reminiscent of early ‘analog computers’: the inflows and states...
are continuous variables, not pulse series or pulse counts. The DKM consists of two inflow–outflow units (IOUs), allocated for the representation of duration perceived during the ‘presentation’ phase and the ‘reproduction’ phase, respectively (Fig. 1). An IOUs state \( y \) evolves in time \( t \) according to the differential equation

\[
\frac{dy}{dt} = i - \kappa y, \quad y_0 = 0,
\]

i.e., the unit acts as a ‘leaky accumulator’\(^1\) of inflow \( i \). There is no built-in metric of accumulated states; the states of the 1st and 2nd accumulator can be only compared; the equality of states, \( y_1(1) = y_2(2) \), is subjectively experienced as ‘equality of durations.’ The DKM is not a computational device; it is rather a primitive comparator of two elapsed time intervals, built upon elementary biological principles.\(^2\)

The dual klepsydra model yields a so-called ‘klepsydraic reproduction function’ (KRF)\(^3\), predicting the reproduction response \( r \) to depend on the stimulus duration \( s \) and the delay \( w \) between the presentation and the reproduction phase, \( r = \text{krf}(s, w) \), where

\[
\text{krf}(s, w) = k^{-1} \ln(1 + \eta(1 - e^{-\kappa s})e^{-\kappa w}).
\]

Here, \( \kappa \) is the ‘loss rate’ coefficient as in Eq. (1), and \( \eta = i_1/i_2 \) is a ratio between the inflows \( i \) into the 1st and 2nd accumulator. Using the same sensory stimulus to mark both intervals, we postulate equal inflow rates, \( i_1 = i_2 \). With \( \eta \equiv 1 \) fixed by postulate, and \( w \) being constant by experimental design, the form of the response function is determined solely by parameter \( \kappa \). The partial functions:

\[
f_\kappa(s) = \text{krf}(s, w|\eta = 1) = 1
\]

constitute a one–parametric family with parameter \( \kappa \geq 0 \), including the ‘chronometrically correct’ reproduction \( r = s \) as a limiting case for \( \kappa \to 0 \). Given \( n \) stimulus–response pairs \( (s_j, r_j)_{j=1...n} \), parameter \( \kappa \) can be estimated by minimizing the weighted sum of squared errors (WLSQ):

\[
E(\kappa) = \sum_{j=1...n} g(s_j)(r_j - f_\kappa(s_j))^2.
\]

The weighting function \( g \) compensates for the increase of response variance with increasing stimulus duration \( s \)\(^4\); we routinely use \( g(s) = s^{-1} \).

The functions (3) match experimental data with very good accuracy, and fit well with the ‘progressive shortening’ phenomenon: the responses \( r \) are typically shorter than presented durations \( s \)\(^5\), and the ratio \( r/s \) decreases with increasing stimulus duration \( s \) (cf. Fig. 3a). This effect, also dubbed ‘subjective shortening’ of temporal intervals in memory\(^2\), is seen as a negative curvature of reproduction curves\(^5\), and clearly revealed by \( r/s \)-versus-\( s \) data plots\(^6\) (cf. Fig. 3b). The ICM can account for the progressive shortening phenomenon only by increasing (effective) pacemaker frequency with time, which itself calls for an explanation. The DKM with constant inflows accounts for this phenomenon naturally, by virtue of the ‘loss term’ \( -\kappa y \) in Eq. (1). The estimates of \( \kappa \) are typically in the range from 0.01 to 0.03 s\(^{-1}\)\(^2\); the higher the value of \( \kappa \), the more pronounced the curvature of the reproduction response curve.

Data from two double-blind, placebo-controlled studies are reported. Experiment 1 was part of a previously published study\(^7\), Reproduction data from that study are re-analysed here, while data from Experiment 2 are presented here for the first time. Psilocybin was administered in gelatine capsules (1 mg and 5 mg), prepared at the Pharmacy of the Cantonal Hospital of Aarau, Switzerland.\(^8\) Lactose placebo was administered in capsules of identical appearance. After oral intake, psilocybin is rapidly transformed to psilocin, the pharmacologically active metabolite. First effects of psilocybin are subjectively perceived 20–40 min after oral intake, reach maximum intensity at about 60–90 min, last for another 60–120 min, and usually vanish within 6–8 h after drug intake\(^7\).

Placebo (P) and two doses of psilocybin were used in Experiment 1, medium (M: 115 µg/kg body weight), and high dose (H: 250 µg/kg body weight), with \( N = 12 \) subjects participating in the study (six men, six women, mean age 26.8 years). Subjects were tested on three separate days (for each condition) with an interval of at least 14 days in between; P, M and H doses were administered in a counter-balanced order. Performance in the timing task was assessed just prior to administration.

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\(^1\) Hence the name of the model: klepsydra = ancient water-clock.

\(^2\) In a tentative neurobiological interpretation\(^2\), Appendix A) the state variable is a relative proportion of excited cells in a neuronal assembly, driven by an excitatory input (‘inflow’). Although there is no direct observational evidence for the DKM, a brain imaging study of temporal reproduction\(^9\) supports the two accumulators hypothesis.

\(^3\) Administration of psilocybin was authorized by the Swiss Federal Office of Public Health, Bern. The experimental procedures were approved by the Ethics Committee of the University Hospital Zürich. Subjects had signed an informed consent, and were reimbursed for their participation in the study.

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of drug/placebo (baseline measures), at 90 min during the anticipated peak effects, and 240 min after drug intake, when effects have decreased substantially (for more details see [28]).

Placebo (P) and a very low dose of psilocybin (VL: 12 μg/kg body weight) were used in Experiment 2, with \( N = 9 \) participants (five men, four women, mean age 48.2 years) and one measurement at \( T = 90 \) min. The two sessions for the respective conditions were separated by at least 14 days and included the same psychometric tests as employed in Experiment 1 [28].

In this low dose study, only few volunteers noticed a difference in state of consciousness or mood between placebo and psilocybin as measured with the Altered States of Consciousness Rating Scale and the Adjective Mood Rating Scale (AMRS), the only observed effect being an increase in the AMRS scale ‘introversion.’

The duration reproduction task (DRT) followed the same design in both experiments. A 500 Hz tone was presented to subjects via headphones for a defined duration \( s \) (presentation phase); after a constant interval of silence, \( w = 2 \) s, the same tone was presented again and the subjects had to switch off the tone by pressing a key when the duration of the second tone was subjectively equal to that of the first tone (reproduction phase). Tone durations \( s = 1.5, 2, 2.5, 4, 4.5, \) and \( 5 \) s were presented in random order, with eight repetitions for each \( s \)-duration. Response times \( r \) were measured with 1 ms precision and averaged over the eight repetitions. An individual DRT data-set for each subject and condition thus consisted of six stimulus–average response pairs \( (s_j, r_j)_{j=1...6} \). For each data-set, parameter \( \kappa \) was estimated by the WLSQ method (4) [3]; the estimates are indicated by a superscripted caret, \( \hat{\kappa} \).

The design of Experiment 1 should result in 3 doses \( \times 3 \) time points \( \times 12 \) subjects = 108 DRT data-sets. Five data-sets of the total of 108 were unavailable due to a computer failure. Nine of the 103 estimates resulted in \( \hat{\kappa} = 0 \), indicating a bad KRF-to-data fit.\(^4\) The non-zero estimates were in the range from 0.0017 to 0.056 s\(^{-1}\) (median \( \approx 0.015 \) s\(^{-1}\)), in good agreement with estimates from other DRT studies. Because of the failed estimates, a total of 14 cells were missing from the data matrix. The treatment of the missing values is explained below, together with the description of subsequent statistical analyses. Experiment 2 yielded 2 doses \( \times 1 \) time point \( \times 9 \) subjects = 18 DRT data-sets. All individual data-sets were available, and all estimates \( \hat{\kappa} \) positive, in the range from 0.0013 to 0.04 s\(^{-1}\) (median \( \approx 0.02 \) s\(^{-1}\)), so there were no missing entries; one subject was post hoc excluded (see footnote 5).

To evaluate net time-dependent effects while discarding inter-individual differences, each subject’s \( \hat{\kappa}s \) were transformed, separately for each drug dose, to intra-individual ratios:

\[
q_T = \frac{\hat{\kappa}_T}{\kappa_0}.
\]  

Here \( \hat{\kappa}_T \) stands for the estimate \( \hat{\kappa} \) from DRT data measured at time \( T = 0, 90, \) or 240 min. Therefore, the initial value \( q_0 = 1 \) for all subjects in all conditions (not entering the statistics), while \( q_90 \) and \( q_{240} \) are comparable across subjects. Where one of the three values \( \hat{\kappa}_0, \hat{\kappa}_90, \hat{\kappa}_{240} \) was unavailable due to technical failure or bad fit (five cases), the missing value was replaced by the geometric mean of the two known values. Where two of the three values were unavailable (three cases), they were replaced by the only one known value; this results in \( q_0 = q_90 = q_{240} = 1 \), i.e. in favor of the null-hypothesis. The same replacement was used in one case where all three values were unavailable due to bad fit.

In Experiment 2, DRT measurements were performed only at \( T = 90 \) min. Therefore, ratios (5) are not applicable, and we can only evaluate the drug effects with respect to (w.r.t.) the placebo condition, via intra-individual ratios:

\[
q_{VP} = \frac{\hat{\kappa}_{90}(VL)}{\hat{\kappa}_{90}(P)}.
\]  

The ratios (5), respectively (6), were log-transformed to remove the asymmetry of their distribution, and submitted to one-sample, two-tailed \( t \)-tests against zero (Table 1). The last line in Table 1 (\( \hat{q} \)) shows anti-log-transformed means = geometric mean of individual \( q’s; \) values higher/lower than 1 indicate a decrease/increase of \( \kappa \) w.r.t. the initial value \( \kappa_0 \) or, respectively, to the placebo value \( \hat{\kappa}_{90}(P) \).

In Experiment 1 at the time of the maximal drug action, \( T = 90 \) min from intake, the medium dose of psilocybin slightly increased the value of \( \hat{\kappa} \) by \( \approx 16\% \), whereas the high dose significantly (\( P < 0.02 \)) increased the value of \( \hat{\kappa} \) by \( \approx 44\% \) (Fig. 2a). Due to our conservative treatment of missing values, the mean log \( q \) was pulled toward 0, so the real effects may be somewhat larger. No significant effects were found at time \( T = 240 \) min from intake, except for the decrease of \( \kappa \) under placebo (\( P \approx 0.05 \)). If this is a real effect, it could reflect the progressive practice in the reproduction task, leading to more precise responses and thus counter-acting the ‘subjective shortening’ of reproduced times, assessed by parameter \( \kappa \). In Experiment 2, duration reproduction at time \( T = 90 \) min from drug intake revealed a significantly higher value of \( \hat{\kappa} \), by \( \approx 83\% \), compared to placebo.\(^5\) Interestingly, this effect was observed with a very low dose of psilocybin, which barely affected self-reported subjective experience.

The effect measures used to evaluate data from Experiments 1 and 2 have been defined differently and are not directly comparable (see Eqs. (5) and (6)). The two reported studies were carried out with groups of participants differing significantly in their age (Experiment 1: mean 26.8 years; Experiment 2: mean 48.2 years). There is evidence for age-dependent decrease of 5-HT\(_{2A}\) receptor expression level [13,16], so that older subjects may show higher sensitivity to psilocybin in terms of cognitive effects. For all these reasons, we refrain from interpretation of different effect sizes between Experiments 1 and 2.

\(^4\) In case of a peculiarly shaped individual response curve (positive curvature), the error functional (4) attains a minimum at the lowermost boundary of the parameter domain, i.e., \( \kappa = 0 \); negative \( \kappa \) values are physically meaningless.

\(^5\) The values shown in Table 1, column Experiment 2, are based on a subset of \( N = 8 \) subjects, after removing one subject with \( q \approx 15.4 \) as an obvious outlier. The entire group’s statistics (\( N = 9 \)) was: mean log \( q = 0.365\), S.D. log \( q = 0.424\), \( t = +2.581\), \( P = 0.033 \). The removal of the extreme value acts in favor of the null-hypothesis, yet the reported effect remains significant.
Table 1
Summary of psilocybin effects on $q$ ratios in the two reported experiments

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>Experiment 1</th>
<th>Experiment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T$ [min]</td>
<td>90</td>
<td>240</td>
<td>90</td>
</tr>
<tr>
<td>Mean log $q$</td>
<td>$-0.018$</td>
<td>$-0.164$</td>
<td>$+0.066$</td>
</tr>
<tr>
<td>S.D. log $q$</td>
<td>$0.326$</td>
<td>$0.261$</td>
<td>$0.194$</td>
</tr>
<tr>
<td>$t$</td>
<td>$-0.196$</td>
<td>$-2.174$</td>
<td>$1.171$</td>
</tr>
<tr>
<td>$P$</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>$\hat{q}$</td>
<td>$0.958$</td>
<td>$0.686$</td>
<td>$1.163$</td>
</tr>
</tbody>
</table>

The present results clearly indicate the applicability of the dual klepsydra model to duration data in the supra-second domain. The estimates of the ‘loss rate’ $\kappa$ are in good agreement with our earlier estimates [21,23], in spite of a relatively narrow variation range of durations used in the two reported studies. Psilocybin, a substance known to strongly influence the subjective experience of time, was found to increase the loss rate of internal time representation. The effect proved to be dose dependent in Experiment 1, where two different doses were compared (Fig. 2 b). In Experiment 2, a significant increase under a very low dose of psilocybin w.r.t. placebo was found (Fig. 3). The DKM parameter $\kappa$ appears to be a fairly sensitive measure of effects of psychoactive substances upon the internal representation of time. The interpretation of these findings in terms of underlying neural mechanisms is not yet clear, as too little is known about the sensitivity of the hypothetical ‘accumulators’ to environmental or organismic factors.

The reported findings may help to understand qualitative alterations of time experience, such as ‘time standing still’ reported from experimentally-induced ASCs [11], mystical or ecstatic states (nunc stans), or in psychopathology [15,10]. The range of reliable perception of temporal order is determined by an interplay between the relaxation time $\kappa^{-1}$ of the DKM accumulators, and the ‘diffusion time’ given by the signal-to-noise ratio of the influx [26]. A simultaneous increase of the influx noise and of the loss rate may cause a fusion of the ‘inner’ and ‘outer’ horizons of duration experience [25], resulting in a total loss of cognition of temporal order (“passage of time”).

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Appendix A. Supplementary Data


References


[3] Details are provided in supplementary files supl-stat.pdf (descriptive statistics of responses) and supl-flts.pdf (measures of goodness-of-fit to the data).


