Neuropsychopharmacology (2005) 30, 1154–1162

www.neuropsychopharmacology.org

Modulating the Rate and Rhythmicity of Perceptual Rivalry Alternations with the Mixed 5-HT_{2A} and 5-HT_{1A} Agonist Psilocybin

Olivia L Carter*[,1,2], John D Pettigrew[1], Felix Hasler[2], Guy M Wallis[3], Guang B Liu[1], Daniel Hell[4] and Franz X Vollenweider[2,4]

[1]Vision Touch and Hearing Research Center, School of Biomedical Science, University of Queensland, Australia; [2]Heffter Research Center, University Hospital of Psychiatry, Zurich, Switzerland; [3]Perception and Motor Systems Lab, School of Human Movement Studies, University of Queensland, Australia; [4]Neuropsychopharmacology and Brain Imaging, University Hospital of Psychiatry, Zurich, Switzerland

Binocular rivalry occurs when different images are presented simultaneously to corresponding points within the left and right eyes. Under these conditions, the observer's perception will alternate between the two perceptual alternatives. Motivated by the reported link between the rate of perceptual alternations, symptoms of psychosis and an incidental observation that the rhythmicity of perceptual alternations during binocular rivalry was greatly increased 10 h after the consumption of LSD, this study aimed to investigate the pharmacology underlying binocular rivalry and to explore the connection between the timing of perceptual switching and psychosis. Psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine, PY) was chosen for the study because, like LSD, it is known to act as an agonist at serotonin (5-HT)$_{1A}$ and 5-HT_{2A} receptors and to produce an altered state sometimes marked by psychosis-like symptoms. A total of 12 healthy human volunteers were tested under placebo, low-dose (115 μg/kg) and high-dose (250 μg/kg) PY conditions. In line with predictions, under both low- and high-dose conditions, the results show that at 90 min postadministration (the peak of drug action), rate and rhythmicity of perceptual alternations were significantly reduced from placebo levels. Following the 90 min testing period, the perceptual switch rate successively increased, with some individuals showing increases well beyond pretest levels at the final testing, 360 min postadministration. However, as some subjects had still not returned to pretest levels by this time, the mean phase duration at 360 min was not found to differ significantly from placebo. Reflecting the drug-induced changes in rivalry phase durations, subjects showed clear changes in psychological state as indexed by the 5D-ASC (altered states of consciousness) rating scales. This study suggests the involvement of serotonergic pathways in binocular rivalry and supports the previously proposed role of a brainstem oscillator in perceptual rivalry alternations and symptoms of psychosis.
Neuropsychopharmacology (2005) **30,** 1154–1162, advance online publication, 26 January 2005; doi:10.1038/sj.npp.1300621

INTRODUCTION

Understanding the neural underpinnings of consciousness has long been a goal of neuroscientists. To this end, considerable attention has been focused recently on different forms of perceptual rivalry as it is a phenomenon characterized by switches in perception that occur despite a constant, if ambiguous, sensory input. Binocular rivalry is a specific form of perceptual rivalry that results when two different images are simultaneously presented to the corresponding retinal location in the left and right eye (Wheatstone, 1838; Walker, 1975). Under these conditions, the observer will experience alternations between awareness and suppression of the two 'rivaling' images. Currently, the debate is focused on the relative influences of early *vs* late visual processes (Blake and Logothetis, 2002), with the majority of research using a variety of imaging (Kleinschmidt *et al*, 1998; Tong and Engel, 2001) and recording (Leopold and Logothetis, 1996; Tononi *et al*, 1998) techniques aimed at identifying the location and nature of neuronal activity that 'correlates' with perceptual awareness and suppression. Relatively little has been done, however, to investigate either the nature of the 'switch' that drives the alternations in visual awareness or the pharmacology underlying the rivalry process. This study aims to look specifically at both of these areas.

Apart from its relevance to consciousness research, binocular rivalry is also of clinical relevance as it has been suggested that perceptual switches characteristic of all forms of rivalry reflect the activity of an oscillator, whose rhythms are fundamental to a number of brain functions

*Correspondence: Ms OL Carter, Heffter Research Center, University Hospital of Psychiatry, Lenggstr. 31 8029 Zurich, Switzerland, Tel: +41 1384 2750, Fax: +41 1 384 3396, E-mail: o.carter@uq.edu.au
Received 28 June 2004; revised 1 October 2004; accepted 5 October 2004
Online publication: 19 October 2004 at http://www.acnp.org/citations/NPP101904040299/default/pdf

and associated variations in conscious state (Pettigrew, 2001). In support of this proposal, it has been shown that extreme deviations from the norm in rivalry rate correspond with symptoms of psychosis (Pettigrew and Miller, 1998; Leonard *et al*, 2001; Miller *et al*, 2003). Further strengthening this link between deviations in perceptual rivalry rhythm and fluctuations in conscious state was the incidental observation that the rhythmicity of perceptual alternations during binocular rivalry was greatly increased 10 h after the reported consumption of LSD (Carter and Pettigrew, 2003). This subject showed a rhythmic, multimodal pattern of harmonic and forbidden intervals, with perceptual switches occurring only after a duration of around 0.9, 1.8, 2.8, or 3.7 s, while few switches were reported after 0.5, 1.5, or 2.5 s. In line with this observation, there was a recent study showing that ayahuasca, a dimethyltryptamine-containing hallucinogenic brew made from psychoactive plants from the Amazon, significantly alters the rate of perceptual switches (Frecska *et al*, 2004).

Specifically, the oscillator model proposes that a number of brainstem nuclei encompassing regions such as the raphe nuclei, the ventral tegmental area, and the locus coeruleus are responsible for the generation of these rhythms in the brain. Each of these nuclei is responsible for the respective release of serotonin (5-HT) (Jacobs and Azmitia, 1992), dopamine (Dahlstrom and Fuxe, 1964) and noradrenalin (Foote *et al*, 1983) into the cortex. The spontaneous, synchronous, and tonic activity characteristic of the neurons in these regions (Aston-Jones and Bloom, 1981; Grace and Onn, 1989; Jacobs and Fornal, 1991) makes them well suited for the generation and propagation of rhythms throughout the brain. In addition, the existence of direct inputs both between these brainstem regions (Pickel *et al*, 1977; Herve *et al*, 1987; Grenhoff *et al*, 1993) and higher cortical areas allows for a system that can be easily modulated by top-down regulation (Svensson and Tung, 1989; Jodo *et al*, 1998; Brown *et al*, 2002). It is proposed that the pacemaker activity of these brainstem nuclei is responsible for pulsatile neurotransmitter release into the cortex, at a rate and rhythm that is modulated both by other brainstem regions and fluctuations in cortical activity. The visual alternations induced during perceptual rivalry are believed to reflect activity of this brainstem oscillator (Pettigrew, 2001).

Given the relevance of the above-mentioned LSD observation to the proposed oscillator model of perceptual rivalry and its link to clinical psychosis, the authors of the current study were motivated to investigate this effect further. However, because LSD is known to act at multiple receptors (5-$HT_{1A/2A}$, D2, and alpha1) with a half-life of $\sim$3.6 h (Lim *et al*, 1988) and an effect time ranging from 8 to 12 h, it was deemed preferable to use psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine, PY), a compound with relatively comparable hallucinogenic properties but greater receptor specificity and a shorter duration of action (half-life $\sim$2.6 h), with symptoms generally dissipating within 4 to 5 h (Hasler *et al*, 1997; Hasler *et al*, 2004).

Receptor binding studies in rats revealed that psilocin (4-hydroxy-*N,N*-dimethyltryptamine), the first and pharmacologically active metabolite of PY (Hasler *et al*, 1997) primarily binds to 5-HT_{2A} receptors (Ki = 6 nM), although with a lower affinity also to 5-HT_{1A} sites (Ki = 190 nM (McKenna *et al*, 1990). In line with this receptor affinity, activation of 5-HT_{2A} receptors leads to a general increase in activity throughout the cortex, believed to be driven predominantly by the induction of glutamatergic excitatory postsynaptic potentials in layer V pyramidal cells of the neocortex (Aghajanian and Marek, 1997). Specifically, this effect is most pronounced in the frontal cortex (Vollenweider *et al*, 1997), where there is an increased density of 5-HT_{2A} receptors as compared to more posterior regions (Wong *et al*, 1987). It has been proposed that the other main effect of PY's activation of the somatodendritic 5-HT_{1A} autoreceptors located on the raphe neurons is an inhibition of tonic firing and associated reduced release of serotonin from this region (Aghajanian and Hailgler, 1975).

On the basis of the known properties of PY and the clearly outlined nature of the proposed brainstem oscillator, a number of predictions were made. (1) That the inhibition of 5-HT release from the raphe nucleus in combination with an increase in cortical activation induced by PY would cause a reduction in the relative influence of the brainstem oscillator and consequently rivalry alternations would become less frequent and less regular. (2) In line with the observed increase in rivalry rhythmicity 10 h after the reported consumption of LSD, it was further speculated that following the peak effects of the drugs, there may be a 'rebound effect' with a reduction in cortical activity leading to increases in the relative 'strength' of the oscillator. (3) Observed effects on rivalry alterations would be associated with subjective changes in conscious state in a dose-dependent manner.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich, and the use of PY was authorized by the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Bern.

Subjects

A total of 12 healthy volunteers (six female and six male) aged between 22 and 33 years (mean 26.8 $\pm$ 3.6 years) were recruited through advertisement from the local university and technical college. After being informed by a written and oral description of the aim of the study, the procedures involved, as well as the effects and possible risks of PY administration, all volunteers were asked to give their written consent as a requirement of participation. All subjects had normal or corrected to normal vision and were healthy according to medical history, clinical examination, electrocardiography, and blood analysis. They were also deemed by psychiatric interview to have no personal or family (first-degree relatives) history of major psychiatric disorder nor evidence for regular alcohol or substance abuse. Six of the participants reported having previous experience with PY through the ingestion of *psilocybe* mushrooms; the other half were PY naïve. Subjects were reimbursed for their time and they were instructed that they were free to withdraw from the study at any time.

Substance and Dosing

PY was obtained through the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Bern. PY capsules (1 and 5 mg) were prepared at the pharmacy of the Cantonal Hospital of Aarau, Switzerland. Quality control comprised tests for identity, purity, and uniformity of content. The PY and lactose placebo were prepared in gelatin capsules of identical appearance. Based on previous PY studies in human volunteers (Vollenweider *et al*, 1998; Hasler *et al*, 2004), the medium (115 μg/kg) and the high dose (250 μg/kg) of PY used in the present study were expected to induce changes in the subject's visual perception without seriously affecting their thought patterns or eroding their self–nonself boundaries. A double-blind placebo-controlled within-subject design with the three different experimental conditions was used. Subjects were tested on three full days, each separated by at least 14 days. On each of the three days subjects received placebo, a low and a high dose of PY respectively, with the order of administration counterbalanced.

Binocular Rivalry

Stationary green vertical and horizontal gratings were presented to the subject's left and right eye, respectively. Viewed from a distance of 60 cm, the gratings had a spatial frequency of 1.5 cycles/degree of visual angle and were presented as a disc that subtended 4° of visual angle. The images were generated in Matlab, using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997) and displayed on an Image System monochrome computer monitor (green, P46 phosphor, persistence = 300 ns). The vertical and horizontal gratings were presented alternately, in rapid succession, at a rate of 120 Hz. Subjects viewed the display through liquid crystal shutters that alternately blocked presentation to the left and the right eye in synchrony with the stimuli. Using this method, it was possible to present the conflicting stimuli to the corresponding retinal location of each eye, without perceptual flicker or crosstalk.

Responses were recorded on a modified computer keyboard. Two raised buttons, one with a ridge aligned perpendicular to the observer and the other running from left to right, were placed on top of the B and V key, respectively. Subjects were instructed to focus only on the orientation of the gratings within the circular patch. Subjects reported the predominance of the vertical gratings by pushing the button with a ridge aligned along a vertical orientation and the predominance of the horizontal gratings by pushing the button on which there was a ridge aligned along a horizontal orientation. If the subject experienced a combination of the two orientations, either as a grid or a patchwork, they were instructed to press the space bar, but only in cases when the mixed percept was stable and not considered to be 'transitional'. Data for each testing period were collected using commercial software (Bireme.com.au) in a block consisting of 4×100 s trials, with subjects receiving a 30 s break between each trial.

In order to insure that subjects understood the task requirements and were capable of reporting their visual experiences accurately during drug-altered states, prior to each binocular rivalry test, they were asked to report their perceptual experience during the presentation of a 1 min movie of simulated rivalry. This 'catch-trial movie' consisted of the sequential presentation of vertical or horizontal gratings (to both eyes). Each respective grating image was identical to the grating stimuli used during the binocular rivalry condition and was presented for between 0.5 and 5 s before being replaced by the grating of the alternative orientation. During this time, subjects were given the same viewing and reporting instructions as those outlined for binocular rivalry. In this way, information regarding response time and accuracy of response was obtained. Four different versions of the catch-trial movie sequence were used throughout the testing in a randomized order.

Psychological Ratings

The German version of the adjective mood rating scale (AMRS) (Janke and Debus, 1978) and the altered state of consciousness (5D-ASC) rating scale (Dittrich, 1998; Dittrich *et al*, 1999) were used to assess the subjective effects under placebo and PY. Both the AMRS and ASC scale had previously been shown to be sensitive to psychological effects of PY in humans (Vollenweider *et al*, 1997, 1998; Hasler *et al*, 2004). The methodology and results pertaining to the AMRS component of this study will not be discussed here as they will be submitted for publication separately.

The 5D-ASC rating scale is a visual-analogue scale that measures alterations in waking consciousness, including changes in mood, perception, experience of oneself and of the environment, as well as disordered thought. The ASC scale consisted of 94 individual statements such as 'I heard tones and noises without knowing where they came from' and subjects were required to mark their current state along a 100 mm line between 'No, not more than normal' or 'Yes, very much more than normal'. Each of the 94 items was given a score from 0 to 100, reflecting the distance of the mark in millimeters from the end indicating no change. The items and their associated scores were grouped to yield five main scales (factors) comprising several item clusters. (1) 'Oceanic Boundlessness' (OB), measures derealization and depersonalization accompanied with changes in affect ranging from heightened mood to euphoria and/or exaltation, and alterations in the sense of time. The corresponding item clusters are 'positive derealization', 'positive depersonalization', 'altered sense of time', 'positive mood', and 'mania-like experience'. (2) 'Anxious Ego Dissolution' (AED) measures ego disintegration associated with loss of self-control, disordered thought, arousal, and anxiety. The item clusters are 'anxious derealization', 'disordered thought', 'delusion', 'fear of loss of thought control', and 'fear of loss of body control'. (3) 'Visionary Restructuralization' (VR) includes the item clusters 'elementary hallucinations' (EH), 'visual (pseudo-) hallucinations' (VH), 'synesthesia' (SY), 'changed meaning of percepts' (CMP), 'facilitated recollection' (FR), and 'facilitated imagination' (FI). (4) 'Auditory Alterations' (AA) refers to acoustic hallucinations and distortions in auditory experiences. (5) The dimension 'Reduction of Vigilance' (RV) relates to states of drowsiness, reduced alertness, and impairment of cognitive function. Subjects completed the 5D-ASC rating scale 110 min after drug administration and were thereby

instructed to rate their whole experience since drug intake (0–110 min).

Experimental Protocol

Before participating in either of the experimental conditions, subjects were taken through each of the measures to insure that they were familiar and comfortable with all tests upon arrival for their first experimental day. For each of the three experiment days, subjects were instructed to have a light breakfast prior to arrival at the hospital. Before testing began, blood pressure and heart rate was measured and subsequently monitored at hourly intervals throughout the day. To obtain baseline scores, subjects were first tested on binocular rivalry. Following this, the placebo/PY was self-administered by oral ingestion. To minimize anxiety, subjects were then advised to relax and allow themselves to become comfortable with any perceptual or cognitive changes experienced. Binocular rivalry was measured again 90, 180, 270, and 360 min after drug intake. After 110 min, subjects were also asked to fill out the 5D-ASC rating scale. Subjects finished participation in the study approximately 7 h after PY consumption and were examined by the principal investigator before being deemed fit to be released.

At a number of intervals throughout the day subjects were additionally tested on time perception and working memory measures. The results from those experiments are not reported here as they will be submitted for publication separately. Subjects were also presented with the KDE ambiguously rotating sphere (Wallach and O'Connell, 1953), for the same 4×100 s trial period used during binocular rivalry. However, throughout the course of the testing sessions subjects reported an increased predominance of the combined percept of two spheres rotating 'inside themselves'. As this became the most dominant percept over the course of testing, it was decided that the rate and rhythm of perceptual alternations could not validly be assessed from the limited remaining data, so results from this portion of the study have not been presented.

Statistical Analysis

For binocular rivalry and the catch-trial movie, significant main effects and interactions of time and dose were determined using Wilks–*Lambda* multivariate test for repeated measures. In the case where significance was found, Tukey's *post hoc* pair-wise comparisons were performed. Drug dose effects were only considered relative to each time point, while 'time of day' or 'effect of repeated test exposure' was considered only for the placebo condition.

To test for significant effects of drug dose on the five ASC scale dimensions (OB, AED, VR, AC, VR), a repeated measures analysis of variance (ANOVA) was used. Given the emphasis of this study on visual perception, an additional repeated measures ANOVA, with treatment (placebo *vs* doses of PY) and VR subscale scores, was conducted to explore whether the different doses of PY produced different patterns of visual alterations. Based on significant main effects or interactions, Tukey's *post hoc* comparisons were performed. All data were analyzed using STATISTICA 6.0 (StatSoft™) for Windows and the criterion for significance was set at $p < 0.05$.

RESULTS

Binocular Rivalry

One subject reported seeing a grid or patchwork combination of the vertical and horizontal gratings for the entire testing period, so the response data from this subject were excluded from the analysis.

Phase duration. The mean phase duration was calculated as the average duration of time (s) that the subject reported uninterrupted dominance of the respective target, for each of the five testing time points. Periods of mixed percept were not included. Significance was found for the main effects of time ($F_{(4,7)} = 7.52$; $p < 0.05$) and dose ($F_{(2,9)} = 6.80$; $p < 0.05$) and a time–dose interaction ($F_{(8,3)} = 9.01$; $p < 0.05$) (Figure 1a). Effects of both gender and prior exposure to PY were considered but were found to have no significant influence on rivalry phase duration ($p = 0.66$ and 0.95, respectively). Subsequent *post hoc* analysis revealed that the phase duration during the low dose condition differed from placebo only at the 'peak' time 90 min postadministration

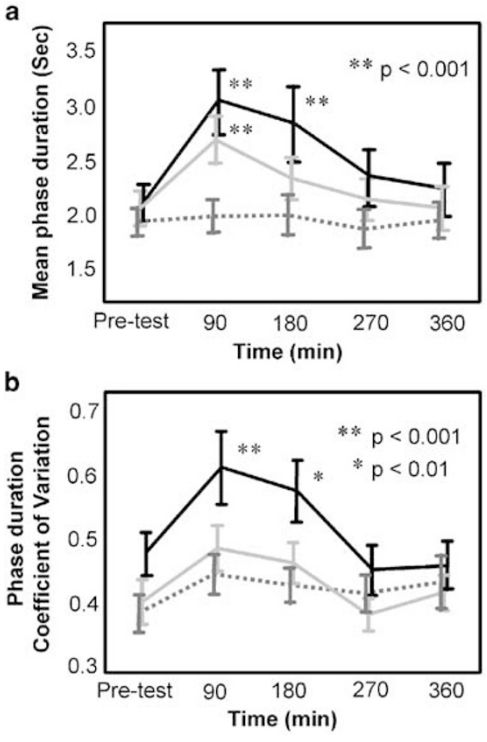

Figure 1 Binocular rivalry phase duration (time between perceptual switches) after administration of placebo (broken dark gray line), low- (light gray), and high- (black) dose PY. (a) Mean phase duration on the high dose of PY was found to be longer compared to placebo at both 90 and 180 min following drug administration. While the phase durations on low-dose PY were significantly longer only at 90 min, compared to placebo. (b) The CV (variance in phase duration relative to the individual's mean duration) for the high dose showed significantly more variability than placebo, at 90 and 180 min. No difference was found between the low dose and the placebo or high dose. Significance is denoted by * for $p < 0.01$ and **for $p < 0.001$, and the bars represent measures of standard error.

(placebo: $\mu = 2.02$, $\sigma = 0.49$; 115 μgPY/kg: $\mu = 2.71$, $\sigma = 0.70$; $p < 0.001$). While the high-dose phase duration was found to be significantly greater than the corresponding placebo measure at both 90 min (250 μgPY/kg: $\mu = 3.04$, $\sigma = 0.95$; $p < 0.001$) and 180 min (placebo: $\mu = 2.04$, $\sigma = 0.61$; 250 μgPY/kg: $\mu = 2.85$, $\sigma = 1.12$; $p < 0.001$), at no single time point was a significant difference observed between the low- and the high-dose condition. No effect of time was observed within the placebo condition.

In order to test whether the overall drug effect size differed significantly between the two dose conditions, effect size was calculated as the mean area under the data–time curve (AUC) for all subjects for each of the three conditions. The AUC values were calculated with respect to relative increase in phase duration from pretest over the entire testing time. To reduce the influence of the substantial degree of between-subject variability, the Page's *L* nonparametric trend analysis (Page, 1963) was performed. A significant difference between the AUC for placebo ($\mu = 4.85$, $\sigma = 74.71$) low dose ($\mu = 86.43$, $\sigma = 102.02$) and high dose ($\mu = 170.75$, $\sigma = 210.14$) was found (Page's $L = 144$; $p < 0.01$).

The total period of time perceiving the mixed percept was found to be slightly greater after administration of PY for both low- and high-dose PY compared to placebo levels; however, neither the effect of time nor dose was found to be significant (time: $F_{(4,7)} = 2.12$; $p =$ NS; dose: $F_{(2,9)} = 1.13$; $p =$ NS).

Coefficient of variation (CV). In order to determine whether there was an effect of time or drug on the regularity/rhythmicity of rivalry alternations, CV values were calculated and compared. Here, the CV represents a measure of variance in rivalry phase duration relative to the individual's mean phase duration. CV was calculated for each subject, and these scores were then averaged to determine the mean CV for each condition. There was a significant main effect of time ($F_{(4,7)} = 15.83$; $p < 0.01$) and dose ($F_{(2,9)} = 9.10$; $p < 0.01$) on CV; however, no time–dose interaction was observed (Figure 1b). *Post hoc* analysis showed that the high-dose condition had significantly more variability compared to placebo, at 90 min (placebo: $\mu = 0.46$, $\sigma = 0.10$; 250 μgPY/kg: $\mu = 0.62$, $\sigma = 0.19$; $p < 0.001$) and 180 min (placebo: $\mu = 0.43$, $\sigma = 0.09$; 250 μgPY/kg: $\mu = 0.58$, $\sigma = 0.16$; $p < 0.01$). No significant difference in CV was found between the low dose and either placebo or the high dose, for any of the five time points. Neither was any difference found between time points within the placebo condition.

Perceptual bias. Proportion of perceptual dominance was unaffected by PY administration. At both the low and the high dose, there was no change in the relative predominance of vertical or horizontal lines experienced (time: $F_{(4,7)} = 1.90$; $p =$ NS; dose: $F_{(2,9)} = 0.18$; $p =$ NS), nor in the absolute magnitude of perceptual predominance (time: $F_{(4,7)} = 3.32$; $p =$ NS; dose: $F_{(2,9)} = 4.23$; $p =$ NS).

Replication of LSD observation. At no time point after administration of PY was there found to be a significant increase in the overall rate or rhythmicity of perceptual switches, nor did any subject show the harmonic-type oscillations seen in the incidental LSD observation that motivated the study (Carter and Pettigrew, 2003). However, looking at the individual data, it can be seen that after the initial increase in phase duration shown by all subjects at 90 min, by 270 min the reported perceptual switches for all subjects became increasingly faster, such that by 360 min some, but not all, subjects were switching at intervals that were shorter and more regular than their pretest levels (Figure 2). Therefore, as some subjects had still not returned to pretest levels at this final testing time, it is not possible to know from these data if this 'rebound' increase in rate would have eventually been observed in all subjects if testing had been extended.

Rivalry pretest catch trials. Key press responses to the perceptual switches presented in the rivalry catch-trial movie were assessed with respect to response accuracy (total number of incorrect responses) for each individual and response time (average elapsed time between image presentation and key press). Response accuracy was not affected by dose ($F_{(2,10)} = 0.48$; $p =$ NS) or time ($F_{(4,8)} = 1.67$; $p =$ NS) (Figure 3a). For response time, there was a significant main effect of time ($F_{(4,8)} = 20.92$; $p < 0.001$) and dose ($F_{(2,10)} = 5.52$; $p < 0.05$), but no time–dose inter-

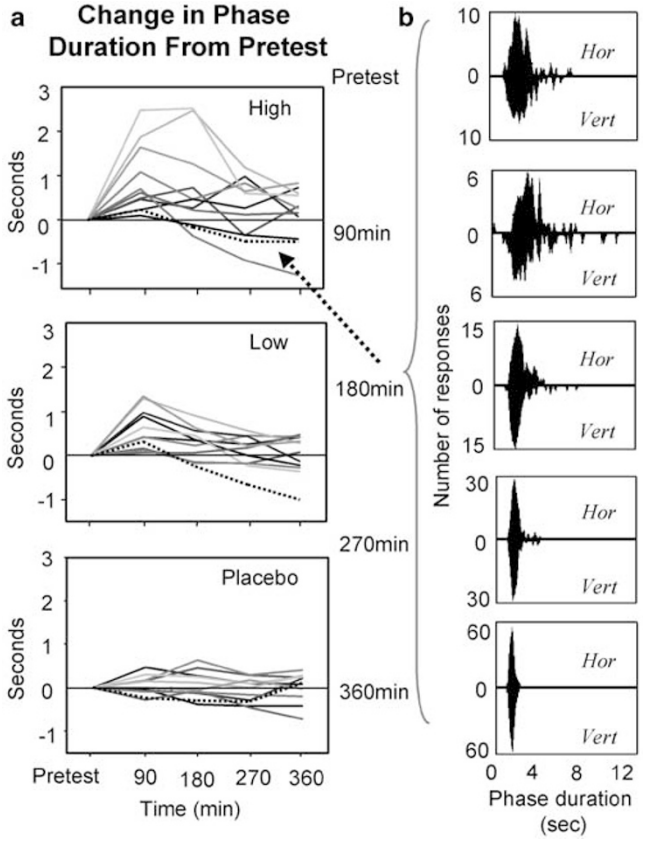

Figure 2 Investigating the 'rebound' increase in binocular rivalry rate and rythmicity as observed in the previously published LSD observation. (a) While no significant effect was found across all subjects, some individuals showed an increase in rate of perceptual switches, after the 'peak' 90 min testing, that continued to increase below pretest levels until the 360 min testing. (b) Phase duration histograms for one individual (broken dark gray line) show the initial reduction and subsequent gradual increase in rate and rhythmicity as seen in some individuals.

action (Figure 3b). The response times under the high dose were significantly slower compared to placebo, at 90 min (placebo: $\mu = 0.36$, $\sigma = 0.05$; 250 μgPY/kg: $\mu = 0.49$, $\sigma = 0.10$; $p < 0.001$) and 180 min (placebo: $\mu = 0.34$, $\sigma = 0.05$; 250 μgPY/kg: $\mu = 0.42$, $\sigma = 0.08$; $p < 0.01$). No significant difference was found between the low dose and either placebo or the high dose, for any of the five time points. Neither was any difference found between time points within the placebo condition.

Psychological Ratings

The peak effects of PY on the five main factors of the ASC dimensions compared to placebo are summarized in Figure 4a. PY increased scores of the five ASC factors in a dose-dependent manner, with significant main effects found for drug ($F_{(2,22)} = 23.68$; $p < 0.00001$) and factor ($F_{(4,44)} = 10.79$; $p < 0.0001$), and a treatment × ASC–factor interaction ($F_{(8,88)} = 8.24$; $p < 0.0001$). *Post hoc* analysis revealed that the high dose caused significant increases in each of the five factors (OB: $p < 0.001$; AED: $p < 0.001$; VR: $p < 0.001$; AA: $p < 0.05$; VR: $p < 0.01$), while the low dose of PY significantly increased only scores for OB ($p < 0.01$) and VR ($p < 0.01$) from placebo levels. Subsequent analysis of the ASC item clusters showed that the increase in OB scores after high-dose PY was mainly due to moderate increases in 'derealization phenomena', 'heightened mood', and 'mania-like' symptoms, while the increase in AED was attributable to moderate 'thought disturbances' followed by slight

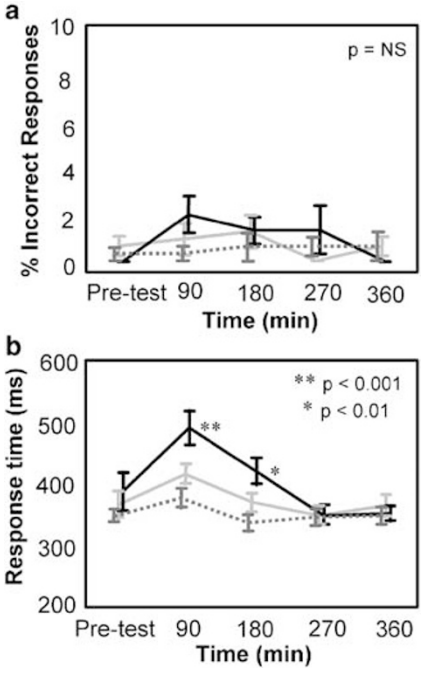

Figure 3 Rivalry pretest catch-trial response for placebo (broken dark gray line), low- (light gray), and high- (black) dose PY. (a) Response accuracy was not significantly affected by either the low or high dose of PY. (b) However, mean response time on the high dose was slower than placebo at 90 and 180 min. The low-dose condition did not differ significantly from either the high dose or placebo. Significance is denoted by * for $p < 0.01$ and ** for $p < 0.001$, and the bars represent measures of standard error.

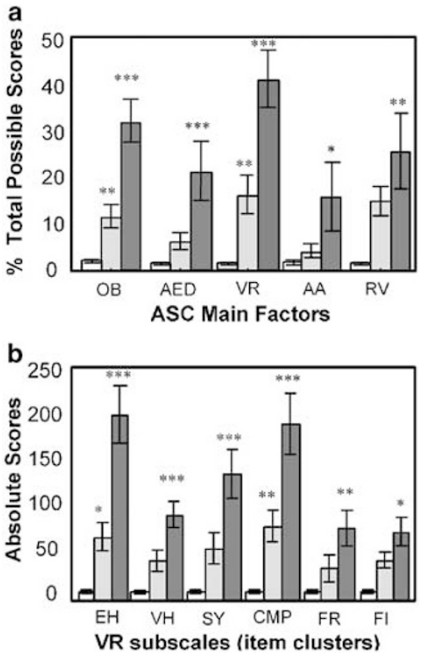

Figure 4 Results from the ASC questionnaire for placebo (white), low- (light gray), and high-dose (dark gray) drug conditions, displaying the subjective effects of drug from the period 0 and 110 min postadministration. Significant difference from placebo levels is denoted by * for $p < 0.05$, ** for $p < 0.01$, and *** for $p < 0.001$, and the bars represent measures of standard error. (a) The percentage of the total possible score for each of the five ASC main factors: OB, and AED, VR, AA, and RV. On the high dose, all factors were significantly higher than placebo, whereas on the low dose only OB and VR, were significantly different from placebo. (b) The scores for each of the six VR subscales: 'EH', 'VH', 'SY', 'CMP', 'FR', and 'FI'. The high dose resulted in a significant increase in each of the six subscales; however, the greatest effects were seen in EH, CMP, and SY. After low-dose PY, only two measures were found to differ significantly from placebo.

increases in 'anxious derealization', 'loss of thought', and 'loss of body' control items. With respect to 'VR' (illustrated in Figure 4b), the high dose resulted in a significant increase in each of the six subscales, with the greatest effects seen in 'EHs' ($p < 0.001$), 'changed meaning of percept' ($p < 0.001$), and 'SY' ($p < 0.001$). The only two measures found to be significantly increased from placebo levels after the low dose of PY were 'EHs' ($p < 0.05$) such as light flashes or geometric figures and 'CMP' ($p < 0.01$).

DISCUSSION

PY acts as an agonist at both the 5-HT_{2A} and 5-HT_{1A} receptors. Activation of these receptor sites simultaneously increases cortical activity (Vollenweider *et al*, 1997), and reduces tonic release of 5-HT from the raphe nucleus (Aghajanian and Hailgler, 1975). As a consequence, it was predicted that administration of PY would lead to a reduction in binocular rivalry switch rate and rhythmicity due to the effective reduction in the relative amplitude of the rhythm generated and a simultaneous increase in the strength of the cortical activity/feedback to the brain stem regions. In line with this prediction, PY was found to dose dependently increase binocular rivalry phase duration in a manner that reflected subjective changes in conscious state.

The mean duration of each successive phase of perceptual dominance (time between switches) was greater than placebo levels 90 min after administration of both the high (250 μg/kg) and low (115 μg/kg) dose of PY. After 180 min, the phase duration remained significantly greater than placebo on the high-dose, but not on the low-dose condition. Using AUC calculations, which combine effect size and duration information, the calculated overall change in phase duration (s) over the entire testing time (min) was found to be dose dependently increased by PY. With respect to regularity of rivalry switches, the mean CV for each subject (variance in rivalry phase duration relative to the individual's mean phase duration) was significantly greater than placebo at both 90 and 180 min on the high dose, but no difference was seen between the low dose and placebo. The harmonic oscillations in perception observed in the subject who subsequently reported taking LSD the night before being tested (Carter and Pettigrew, 2003) were not seen in any subject on either the high or the low dose of this study. However, if the individual data are considered, it can be seen that while phase durations do increase from pretest levels 90 min postdrug intake on the low and high dose, after 180 min all subjects were returning back to pretest. By 270 and 360 min, a number of subjects showed a 'rebound' increase in rate and rhythmicity beyond pretest levels. However, as the majority of subjects had still not returned to pretest levels at this point, the overall effect did not reach significance. These results raise questions about whether or not more subjects would have continued to show reductions in phase duration if testing had been extended out a further 1 or 2 h.

As the alternations in perceptual state are measured indirectly by subjects reporting changes in their visual perception via key press, it could be argued that any inappropriate button response or substantial reduction in reaction time may result in 'missed' switches. However, subjects showed no increase in the percentage of incorrect responses during the pretest 'catch-trial movie' and only a minor increase in response time compared to placebo on the high dose (0.13 s). This is in agreement with subjective reports that the task of determining the relative dominance of vertical and horizontal gratings remained possible, despite the gratings often appearing to fluctuate in color and depth or even taking on human characteristics. For example, one subject commented that the vertical and horizontal gratings appeared to be at war with each other, with each successively 'reclaiming the other's territory'. Consequently, it seems likely that the binocular rivalry effects reported in this study reflect real changes in the individual's perceptual state rather than an inability to perform the task correctly. An alternative criticism to this study is that PY might be influencing rivalry through drug-induced changes of visual sensitivity. This possibility is particularly relevant given that binocular rivalry rate can be slowed down by reducing the relative strength of the stimulus (Levelt, 1965; Fahle, 1982) and PY is known to induce distortions in visual perception. However, results from a second study partly motivated by this concern showed that, while a medium dose of PY (215 μg/kg) impaired coherence sensitivity for random dot patterns, contrast sensitivity for drifting gratings was not effected (Carter *et al*, 2004). This result indicates that the visual disturbances associated with this drug are unlikely to reflect changes at either the retinal level or in the transfer of information from the retina through the lateral geniculate nucleus to the primary visual cortex.

With respect to the relevance of binocular rivalry to symptoms of psychosis, it was predicted that any observed effects on rivalry alterations would be associated, in a dose-dependent manner, with subjective changes in conscious state. In line with this prediction and previous reports (Hasler *et al*, 2004), PY was found to increase scores of the ASC factors in a dose-dependent manner. Compared to placebo levels, the high-dose PY significantly increased each of the five factors: OB, AED, VR, AA, and RV, while the low dose of PY increased only scores for OB and VR in a statistically significant manner. The observation that the degree of effect on the rivalry rhythm paralleled the dose-dependent differences in subjective changes in conscious state induced by PY is in line with the proposed link between deviations in the brainstem rhythms and symptoms of psychosis. It also emphasizes the potential diagnostic value that binocular rivalry might offer the field of psychiatry. In further support of this point, it was noticed that the only subject who showed a mild and transient psychotic reaction to PY also had the greatest deviation of rivalry rate induced by the drug.

While the results of this study are in line with those predicted by the brainstem oscillator model, the authors of the current study acknowledge that standing alone they are not sufficient to rule out other possible mechanisms by which PY may effect rivalry. Rather, this study should be considered as an initial step in understanding the pharmacological interactions underlying conscious perception and suggests that any competing theory of rivalry should be equally able to account for considerable changes in rate associated with such modulations in neurotransmitter levels. With respect to future studies, a number of interesting questions have been raised by the results reported here. The most obvious question is whether PY's influence on binocular rivalry is mediated through either the 5-HT_{1A} or 5-HT_{2A} receptor system exclusively, or if both receptors are involved. As it has been shown previously that the majority of subjective effects induced by PY are blocked by the selective 5-HT_{2A} antagonist ketanserin (Vollenweider *et al*, 1998), it would be particularly interesting to learn whether pretreatment with ketanserin can also block the effects of PY on perceptual rivalry, or if the subjective experience and the perceptual rivalry phenomena can be dissociated.

CONCLUSION

These findings show that the 5-HT_{1A} and 5-HT_{2A} agonist PY dose dependently reduces rivalry rate and rhythmicity in a manner reflecting subjective changes in conscious state. While it is premature to draw any firm conclusions regarding either the physiological basis of binocular rivalry or psychosis on the basis of this result alone, taken in combination with previous studies linking rivalry rate with bi-polar disorder and schizophrenia, it reinforces the idea that the pattern of switching in rivalry may reflect some fundamental processes essential to the maintenance of

normal brain function. These data also show that while the rate of binocular rivalry switches is generally very stable within an individual (Pettigrew and Miller, 1998), this rhythm can be profoundly and reliably altered through pharmacological manipulation. Perhaps, most significantly, this result highlights the need and potential benefit of incorporating the expertise and interests of the relatively independent fields of psychopharmacology, vision science, and mental health in future research into perception and consciousness.

ACKNOWLEDGEMENTS

This investigation was financially supported by the Heffter Research Institute, Santa Fe, New Mexico, USA and a Stanley foundation grant to Jack Pettigrew.

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