Psilocybin impairs high-level but not low-level motion perception

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The hallucinogenic serotonin$_{1A\&2A}$ agonist psilocybin is known for its ability to induce illusions of motion in otherwise stationary objects or textured surfaces. This study investigated the effect of psilocybin on local and global motion processing in nine human volunteers. Using a forced choice direction of motion discrimination task we show that psilocybin selectively impairs coherence sensitivity for random dot patterns, likely mediated by high-level global motion detectors, but not contrast sensitivity for drifting gratings, believed to be mediated by low-level detectors. These results are in line with those observed within schizophrenic populations and are discussed in respect to the proposition that psilocybin may provide a model to investigate clinical psychosis and the pharmacological underpinnings of visual perception in normal populations. *NeuroReport* 15:1947–1951 © 2004 Lippincott Williams & Wilkins.

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INTRODUCTION

Like LSD and mescaline, the serotonergic (5-HT) hallucinogen psilocybin is renowned for its ability to temporarily alter an individual's conscious state. Known for causing visual disturbances, it is often reported that psilocybin causes surrounding objects and colours to appear brighter or clearer, with successively higher doses leading to illusions of motion and colour that can increase in complexity, resulting in elementary geometric and scenic hallucinations [1]. Although psilocybin binds to both 5-HT$_{2A}$ (k_i=6 nmol) and 5-HT$_{1A}$ (k_i=190 nmol) subtypes of serotonin receptors [2], recent evidence demonstrates that psilocybin induces visual distortions via 5-HT$_{2A}$ receptor activation [3]. Accordingly, this drug can be used to induce transient and predictable changes in neurotransmitter activity, in a controlled and selective manner, to gain insight into the mechanisms responsible for visual distortions associated with drug induced and schizophrenia related altered states of consciousness [4,5].

Vision is a fundamental component of the human conscious experience [6]. Consequently, an accurate characterization of where and how hallucinogens, such as psilocybin, influence different stages of visual perception could be beneficial on a number of counts. Given that psilocybin is known to induce illusions of motion, this study was designed to investigate two aspects of motion perception: contrast sensitivity for drifting gratings and coherence sensitivity for drifting random dot patterns. Evidence suggests that contrast sensitivity is limited by an early stage of visual processing, likely to be V1 itself [7,8]. However, the integration of local motion signals necessary for coherent thresholds is probably mediated by higher-level processes and is generally considered to involve the middle temporal area (MT or V5) [8–10]. Neural activity in this region shows strong motion opponency [11], increases linearly with motion coherence [12] and correlates closely with motion perception [13]. Because contrast sensitivity is thought to reflect early visual processes and motion coherence requires higher regions such as MT, the relative influence of psilocybin on these two visual processes can be used as an indication of the effect of this drug on different levels of cortical processing.

The primary aim of this study was to determine whether psilocybin impairs motion processing. A secondary aim was to investigate whether it does so with a selectivity similar to that seen in schizophrenic individuals, as this population has been shown to have deficits in local but not global motion processing [14]. Independent of clinical relevance, the final aim of this study was to use psilocybin's primary and preferential mode of action at 5-HT$_{2A}$ receptors to investigate a possible role of the serotonergic system in visual perception. This is of relevance because despite the

common belief that the visual disturbances characteristics of hallucinogens are mediated predominantly via 5-HT receptors [3,15], to date, most research into the pharmacology of visual deficits in schizophrenic populations has tended to focus on dopamine [16,17].

MATERIALS AND METHODS

Substance and dosing: Psilocybin was obtained through the Swiss Federal Office for Public Health. Psilocybin capsules (1 mg and 5 mg) were prepared at the pharmacy of the Cantonal Hospital of Aarau, Switzerland and quality was controlled through tests for identity, purity and uniformity of content. The psilocybin dose (215 μg/kg) and lactose placebo were administered in gelatine capsules of identical appearance.

Subjects: Nine healthy volunteers (five male, four female) aged between 21 and 31 (mean ± s.d. = 27.1 ± 2.6) 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, and the effects and possible risks of psilocybin 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. Five of the participants reported having previous experience with psilocybin through the ingestion of psilocybe mushrooms; the other four were psilocybin-naive. Subjects were reimbursed for their time and they were instructed that at any time they were free to withdraw from the study. The study was approved by the ethics committee of the University Hospital of Psychiatry, Zurich, and the use of psilocybin in humans was authorized by the Swiss Federal Office for public health.

Stimulus and procedure: Measures of contrast sensitivity were obtained using drifting gratings (Fig. 1). The stimulus comprised a 5 circular patch of vertical, sinusoidal grating with a spatial frequency of 1 cycle/deg, embedded in dynamic random noise. The grating was caused to drift leftwards or rightwards at 20 deg/s (10 Hz). Subjects were instructed to maintain fixation on a central fixation point and attend only to the direction of motion of the gratings within the patch while reporting the drift direction by pressing either the left or right arrow key of the keyboard.

The gratings were generated in Matlab, using the Psychophysics Toolbox extensions [18,19] and presented on the screen for 400 ms (frame rate 100 Hz, mean luminance 30 cd/m^2). The contrast of the gratings was set initially to 30%, and then varied to home in on threshold using the adaptive QUEST algorithm [18,19]. Each session comprised 30 trials, and three sessions were run for each condition.

For the coherence thresholds, the stimuli comprised 100 small dots (each subtending 20′ arc), half black and half white, generated by a C program running in DOS. A proportion of the dots were caused to drift leftwards or rightwards (20 deg/s), while the remainder of dots were displayed at random positions. Coherence thresholds (inverse of coherence sensitivity) were defined as the minimum proportion of coherently moving dots to produce 75% correct direction discrimination. Again, the stimulus was presented for 400 ms and coherence was varied from trial to trial by the QUEST algorithm, giving three separate estimates of threshold, each from 30 trials.

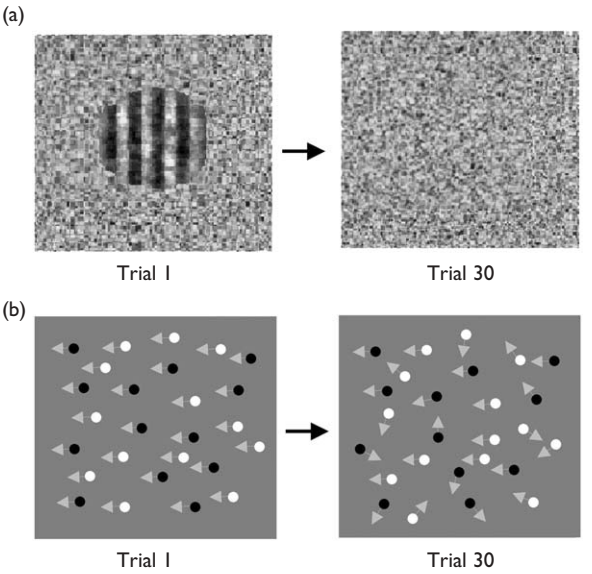

Fig. 1. Experimental stimuli. (**a**) Visual contrast sensitivity was measured by asking subjects to report the direction of motion of a sinusoidal grating embedded within a background of noise. During the 30 trials of the session, the contrast of the gratings was reduced or increased adaptively, depending on whether or not the subject's response was correct. In this way a threshold estimate was calculated: the level of contrast at which motion direction identification was just possible. (**b**) Coherence thresholds for global visual motion were measured with a random – dot pattern where a proportion of dots moved coherently, leftwards or rightwards, while the others were displayed at random. The ratio of coherent to randomly moving dots was varied from trial to home in on the threshold at which direction of motion was just detectable.

All stimuli were presented to subjects on a Sony Trinitron Multiscan E215 monitor and viewed from a distance of 60 cm within a dimly lit room. The final estimates of sensitivity for all conditions were calculated offline by fitting all data of a particular condition (90 trials) with cumulative Gaussian functions, and estimating the level of contrast or coherence to support 75% correct response.

Note that although the speed was matched for both types of stimuli (20 deg/s), the spatiotemporal characteristics were not identical: the stimuli for contrast sensitivity were narrow-band gratings, with a single spatial and temporal frequency (0.5 cycles/deg, 20 Hz), while the coherence stimuli were broadband random-dot patterns, with a range of temporal and spatial frequencies. The motivation for the choice of stimuli was that it was considered that narrow-band stimuli isolate better early motion mechanisms, whereas higher motion mechanisms have a broad range of spatial frequency selectivity [20].

Experimental design and statistical analysis: The study was double-blind, placebo-controlled, the order of dose

assignment was counterbalanced and each experimental day was separated by at least 14 days. On each experimental day subjects were tested on all conditions prior to administration of psilocybin or placebo and then re-tested during the peak effect of the drug ~120 min after administration. In all sessions, subjects repeated the local and global motion discrimination tasks 3 times and the presentation order of these two tasks was sequentially alternated and counterbalanced.

A repeated measures ANOVA was used to determine significance between the log sensitivity values for the respective drug conditions at pre-test and after 120 min for each of the two measures. In the case where significance was found, Tukey's *post-hoc* pair-wise comparisons were performed with α=0.05.

RESULTS

The geometric means for contrast and coherence sensitivity for pre-test and 120 min after drug intake, under both placebo (open bars) and psilocybin (grey bars) conditions are reported in Figure 2. With the contrast sensitivity for moving gratings, no significant time or drug effects were found ($F(1,8)=1.27$; p=NS). There was a slight reduction in average contrast sensitivity for the psilocybin condition at 120 min but the difference between this and the placebo condition was not statistically significant (p=0.58). However, the coherence sensitivities did show a significant effect of time and drug ($F(1,8)=7.39$; $p<0.05$). Subsequent *post-hoc* analysis revealed that the coherence sensitivity 120 min after psilocybin intake was significantly reduced from both the psilocybin pretest measure (p=0.025) and the corresponding 120 min placebo measure (p=0.032).

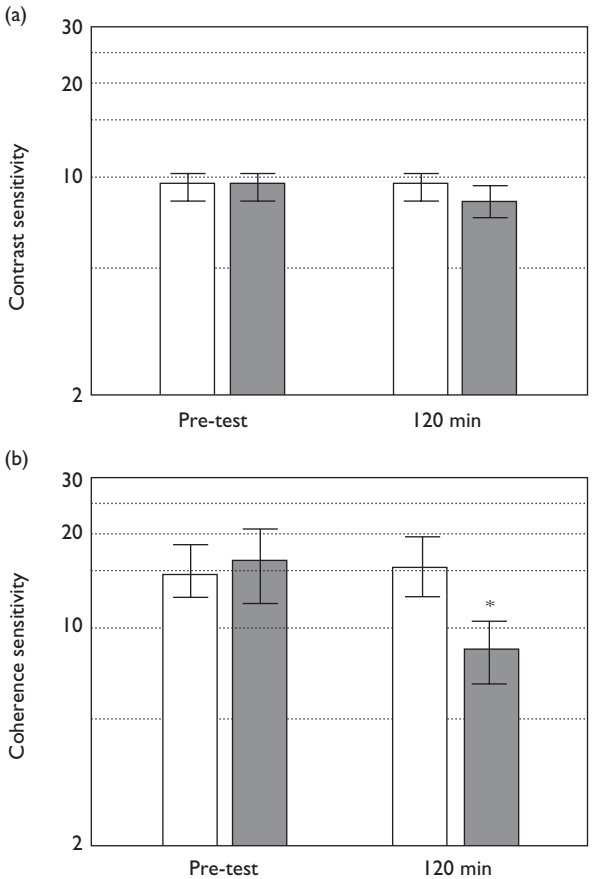

Fig. 2. Psilocybin administration was found to significantly reduce coherence but not contrast sensitivity. The two graphs illustrate the geometric mean for sensitivities at pre-test and peak state, tested 2 h after administration of either placebo (open bars) or psilocybin (grey bars), for (**a**) contrast and (**b**) coherence motion detection respectively. In the psilocybin condition, there is a significant reduction in global motion sensitivity in the 120 min peak condition compared with the pre-test level. No significant differences are observed in the placebo conditions. Error bars represent ± 1 s.e.; *$p<0.05$ level.

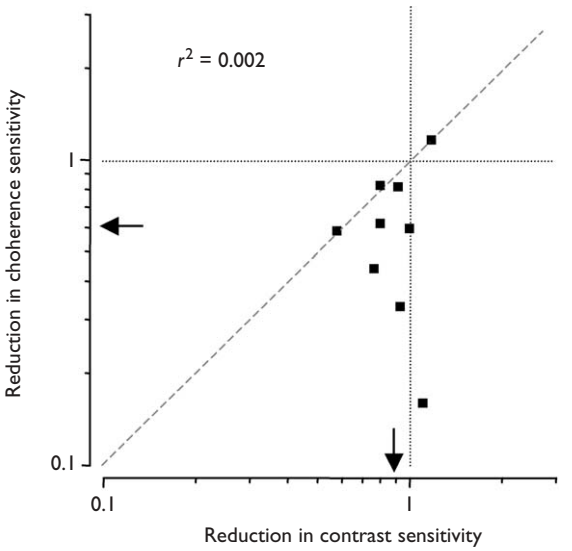

Fig. 3. Individual data showing reduction in relative sensitivity at the peak testing time for coherence sensitivity (ordinate) plotted against contrast sensitivity (abscissa). The estimates of sensitivity reduction were calculated as the ratio of placebo to psilocybin sensitivity in the 120 min peak condition. The arrows show the respective mean reduction in sensitivity. The vertical and horizontal dashed lines passing through unity correspond to no drug effect, while the diagonal line indicates equal effect for the two conditions. Most points pass below this line, indicating greater reduction of coherence than contrast sensitivities.

Figure 3 shows the individual results as a scatter plot, plotting the reduction in coherence sensitivity (ratio of placebo to psilocybin sensitivities) against the reduction in contrast sensitivities. While there is some scatter in the data, most points sit below the equality line (dashed), showing a greater effect for coherence than for contrast sensitivity. There was virtually no correlation (r^2=0.002) between the two estimates of sensitivity, consistent with the fact that one was affected and the other not.

DISCUSSION

Here we show that a 215 μg/kg dose of the 5-$HT_{1A\&2A}$ agonist psilocybin selectively impairs global motion, but not local motion processing in humans. Current evidence suggests that local motion discrimination is resolved at the level of V1 [7,8], while the integration of local motion signals necessary for global motion discrimination is believed to be dependent on higher processing areas such as MT [8,12].

Consumption of psilocybin, in doses similar to those used in the current study, often results in visual and cognitive disturbances (for a detailed psychometric report see [1]). In

this study subjects were encouraged to report their subjective impressions, prior to and after the experimentation. Some reported that surfaces appeared to pulsate in depth or acquire a texture comprising intricate dynamic patterns. Many reported that objects themselves were seen to sway or to protrude further into their surrounding space. Beyond a general warping of perspective, however, the gross spatial organisation of objects and their surrounds remained stable relative to the observer. For example, a plant situated in the corner of the room may appear to be dancing or growing towards the viewer and the room itself may shrink or expand but the room will not spin around the observer nor would the plant appear to hover in space or move to the other side of the room. Subjects reported that the computer keyboard and monitor generally remained stable while dynamic textures and patterns would sometimes be seen both within the background grey component of the display and the target stimulus. Some subjects also reported the stimulus to be flickering. All these reports are in general agreement with previous studies using similar doses [1].

Based on converging evidence it has been suggested that psilocybin-induced altered states of consciousness may provide a model through which to investigate clinical symptoms of psychosis such as those common to schizophrenia [5]. In support of this proposition, our results are in line with previous work showing that schizophrenic individuals are impaired in coherent but not local motion processing, compared to normal populations [14]. Given that psilocybin is known to show relative selectivity as an agonist at the 5-$HT_{1A\&2A}$ receptor sites, this result raises questions regarding the assertion that the motion perception deficits observed in schizophrenic patients are due to differential activation of the dopamine D2 receptor within this population [16]. As both neurotransmitter systems are commonly targeted in anti-psychotic medication, it is important that the relative influence of these transmitters is understood if optimal anti-psychotic medications are to be designed in the future.

In addition to the observed drug induced reduction in coherent motion sensitivity, the fact that psilocybin did not significantly affect local motion contrast sensitivity is a valuable result in itself. First, it shows that subjects were still capable of attending to the stimulus and accurately reporting their perception, whist under the influence of psilocybin. Second, because local motion discrimination is believed to be a relatively low-level process resolvable at the level of V1, the lack of effect on local motion thresholds indicates that the visual disturbances and hallucinations associated with this drug are unlikely to reflect changes either at the retinal level or in the transfer of information from the retina through the lateral geniculate nucleus (LGN) to primary visual cortex.

It is currently unclear to what degree psilocybin effects the vestibular system and this is an additional area that may be worth investigating in the future, particularly in light of a recent paper by Jeong *et al*. indicating that vestibular nuclei may be activated by the 5-HT_2 receptors [21]. However, given that subjects had no trouble moving around their environment and the experimenter observed no evidence of nystagmus or any other systematic changes in eye movements, it seems unlikely that the illusions of motion described here result from vestibular dysfunction. Furthermore, the reported illusions of motion were confined to specific objects, not gross translations of the whole visual field, or sensations of self motion, as would be expected from disturbance of the vestibular system.

As a number of subjects commented that subjectively the global motion task became harder due to an increased salience of the randomly moving dots, one avenue for future research is the question of whether the coherent motion deficit induced by the psilocybin reflects a reduction in sensitivity to motion signals or reduced inhibition of the non-coherent motion signals. Further investigation of this distinction between reduced sensitivity to the motion signals of interest, as opposed to a reduction of inhibition of the noise (increasing the interference/distraction) caused by the non-coherent motion, is of particular relevance given the hypothesized role of sensorimotor gating deficits in schizophrenia [5].

Because the stimulus presentation time in the current study was 400 ms, an alternative explanation to be considered is that psilocybin causes a reduction in temporal integration. It has been shown that for local motion processing, performance improves linearly as stimulus presentation increases up until about 200 ms, whereas for global motion processing performance continues to improve with increased stimulus exposure durations of up to 3 s [22]. It is possible that psilocybin acts to reduce this limit in a similar way that it is known to vary with attentional load [23]. The issue of temporal integration is worthy of further investigation as it is of relevance to the observed motion processing deficits in clinical populations, as well as the psilocybin induced effects reported here.

To date, investigations into visual consciousness has focused on identifying the aspects of neural activity which correlate with perception, whilst little attention has been paid to understanding the integral role of the neurotransmitters in modulating this neural activity. This work illustrates that drugs that transiently alter an individual's visual perception may offer one means to explore the pharmacological processes underlying vision and redress this imbalance.

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