Using Psilocybin to Investigate the Relationship between Attention, Working Memory, and the Serotonin 1A and 2A Receptors

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Abstract

■ Increasing evidence suggests a link between attention, working memory, serotonin (5-HT), and prefrontal cortex activity. In an attempt to tease out the relationship between these elements, this study tested the effects of the hallucinogenic mixed 5-$HT_{1A/2A}$ receptor agonist psilocybin alone and after pretreatment with the 5-HT_{2A} antagonist ketanserin. Eight healthy human volunteers were tested on a multiple-object tracking task and spatial working memory task under the four conditions: placebo, psilocybin (215 μg/kg), ketanserin (50 mg), and psilocybin and ketanserin. Psilocybin significantly reduced attentional tracking ability, but had no significant effect on spatial working memory, suggesting a functional dissociation between the two tasks. Pretreatment with ketanserin did not attenuate the effect of psilocybin on attentional performance, suggesting a primary involvement of the 5-HT_{1A} receptor in the observed deficit. Based on physiological and pharmacological data, we speculate that this impaired attentional performance may reflect a reduced ability to suppress or ignore distracting stimuli rather than reduced attentional capacity. The clinical relevance of these results is also discussed. ■

INTRODUCTION

In a world where objects and events occurring around us have varying degrees of relevance and importance, the ability to selectively direct and maintain attention on a sample of relevant events at the expense of events classed as irrelevant is an obvious advantage. However, given the cost and benefits associated with either attending or not attending to any given stimulus, a discriminative balance between selectivity and breadth is needed. Accordingly, a number of clinical conditions such as obsessive–compulsive disorder (Clayton, Richards, & Edwards, 1999), autism (Sturm, Fernell, & Gillberg, 2004), attention deficit disorder (Barkley, 1997), and schizophrenia (Addington & Addington, 1998; Nuechterlein & Dawson, 1984) have all been associated with attentional abnormalities.

In respect to the maintenance and division of attention, early theorists proposed that there could only be a single focus, functionally analogous to a spot light (e.g., Posner, Snyder, & Davidson, 1980; Eriksen & Hoffman, 1972) or zoom lens (Eriksen & St James, 1986). However, more recent work has shown that it is possible to simultaneously track multiple objects distributed throughout space (Pylyshyn & Storm, 1988), independent of eye movements (Culham et al., 1998). An increasing number of studies are attempting to investigate the neural underpinnings of multiple-object tracking. This work includes an fMRI study implicating a role for regions of the frontal cortex (Culham, Cavanagh, & Kanwisher, 2001), whereas psychophysical studies have been concerned primarily with the relative involvement of feature-based (Scholl, Pylyshyn, & Feldman, 2001; Yantis, 1992) and space-based cues (Somers, Dale, Seiffert, & Tootell, 1999; Luck, Chelazzi, Hillyard, & Desimone, 1997). Despite this recent work, a basic understanding of the attentional processes remains elusive. Here we use a pharmacological approach in an attempt to gain some insights into the mechanisms involved.

Psilocybin, the main hallucinogenic compound found in *Psilocybe* mushrooms, is the primary focus of this study as it is known to transiently alter an individual's cognitive and perceptual state (Carter, Pettigrew, Hasler, et al., 2005; Carter, Pettigrew, Burr, et al., 2004; Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004; Umbricht et al., 2003). The characteristic capability of this drug to induce altered states of consciousness is believed to result from its ability to functionally mimic the

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endogenous neurotransmitter serotonin (5-HT) at selective receptor sites. Receptor binding studies in rats have shown that psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine), the pharmacologically active metabolite of psilocybin (Hasler, Bourquin, Brenneisen, Bar, & Vollenweider, 1997), primarily binds to 5-HT_{2A} receptors (K_i = 6 nM) and with a lower affinity also to the 5-HT_{1A} sites (K_i = 190 nM) (McKenna, Repke, Lo, & Peroutka, 1990). The 5-HT_{2A} receptors are located predominantly on the apical dendrites of pyramidal cells of the cortex (Jakab & Goldman-Rakic, 1998), with activation of these receptors leading to increased cortical activity believed to be driven by glutamatergic excitatory postsynaptic potentials, particularly in Layer V (Aghajanian & Marek, 1997). 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). In contrast, the 5-HT_{1A} receptors are localized presynaptically as somatodendritic autoreceptors in the raphe nucleus of the brainstem (Sotelo, Cholley, El Mestikawy, Gozlan, & Hamon, 1990). Activation of these receptors inhibits the firing of raphe neurons and associated release of 5-HT into the cortex (Sprouse & Aghajanian, 1986; Aghajanian & Hailgler, 1975). Concentrations of postsynaptic 5-HT_{1A} receptors have also been identified in the hippocampus (Hamon et al., 1990) and in the pyramidal cells of the prefrontal cortex (Glaser, Rath, Traber, Zilles, & Schleicher, 1985; Pazos & Palacios, 1985), where they have been found to inhibit pyramidal cell activity in a manner proportional to 5-HT release from the raphe (Puig, Artigas, & Celada, 2005). Therefore, psilocybin increases activation of the prefrontal cortex on two counts: directly via activation of the 5-HT_{2A} receptor and indirectly via the reduced inhibition of pyramidal cell activity in the prefrontal cortex as a consequence of the reduction in 5-HT release from the raphe.

To our knowledge, the current study is the first attempt to look at the pharmacology underlying attentional tracking, or any task analogous to it. However, many human and animal studies suggest that serotonin (5-HT) and the 5-HT_{1A} receptor may be relevant to attention. For example, human studies have shown that 5-HT depletion leads to impairment of go/no-go tasks requiring attentional set shifting and related inhibition of attentional set (Rubinsztein et al., 2001). In rats, studies of attention have focused primarily on measures of impulsivity, such as the five-choice serial reaction time task (Carli, Robbins, Evenden, & Everitt, 1983). Using this paradigm, direct administration of the 5-HT_{1A} agonist 8-OH-DPAT into the prefrontal cortex was found to improve attentional performance (Winstanley et al., 2003). However, both indirect administration of the same compound (Carli & Samanin, 2000) and global 5-HT depletion (Harrison, Everitt, & Robbins, 1997) resulted in impaired performance on the same task. This suggests that if activation of the 5-HT_{1A} receptors is not limited to the prefrontal cortex, the overall reduction in the release of 5-HT from the raphe that results from activation of the presynaptic 5-HT_{1A} receptors in this region will lead to an impairment of attention.

There is considerable anecdotal evidence that attentional processes are affected by psilocybin (i.e., Shulgin & Shulgin, 1997; McKenna, 1992) and formal self-rating scales indicate that psilocybin can cause a subjective reduction in vigilance (Hasler et al., 2004). However, only one study has attempted to assess the effect of psilocybin on attention objectively. Gouzoulis-Mayfrank et al. (2002) examined both reaction time and covert orienting of attention. Although the authors highlight the preliminary nature of their findings, the observed effects of psilocybin were interpreted as indicating a difficulty in disengaging attention from previously attended locations.

The purpose of the current study was to investigate the effects of psilocybin on attentional function using a task that does not require a speeded reaction time response, which may be affected by motor control or other nonattentional factors. Partially motivated by subjective reports in which subjects believe they have an increased capacity to monitor many elements, we chose a multiple-object tracking task similar to that used by Pylyshyn and Storm (1988) (Figure 1A). The task required subjects to track a subset (up to 8) of 20 visually indistinguishable randomly moving green dots and is believed to test an individual's capacity to maintain multiple focuses of attention simultaneously (cf. Alvarez, Horowitz, Arsenio, DiMase, & Wolfe, in press). As it has been suggested that the maintenance or direction of attention over time involves working memory (Oksama & Hyona, 2004; Desimone, 1998) and both processes are believed to be subserved by similar regions of the prefrontal cortex (Culham et al., 2001; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998), we were also interested in whether changes in the performance of spatial working memory might also arise. To test spatial working memory, an electronic version of Corsi's block tapping task was used (Milner, 1971) (Figure 1B). In this task, subjects were required to remember and reproduce a sequence of (up to 9) spatial locations. This measure of working memory was chosen because performance on the task had previously been shown to be sensitive to administration of psilocybin (Wittmann et al., submitted).

Psilocybin is known to activate both 5-HT_{1A} and 5-HT_{2A} receptor subtypes. However, the majority of the drug's subjective effects are generally attributed to activation of the 5-HT_{2A} receptor (Nichols, 2004; Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998). Therefore, an additional goal of the current experiment was to investigate whether blockade of this receptor with the selective 5-HT_{2A}

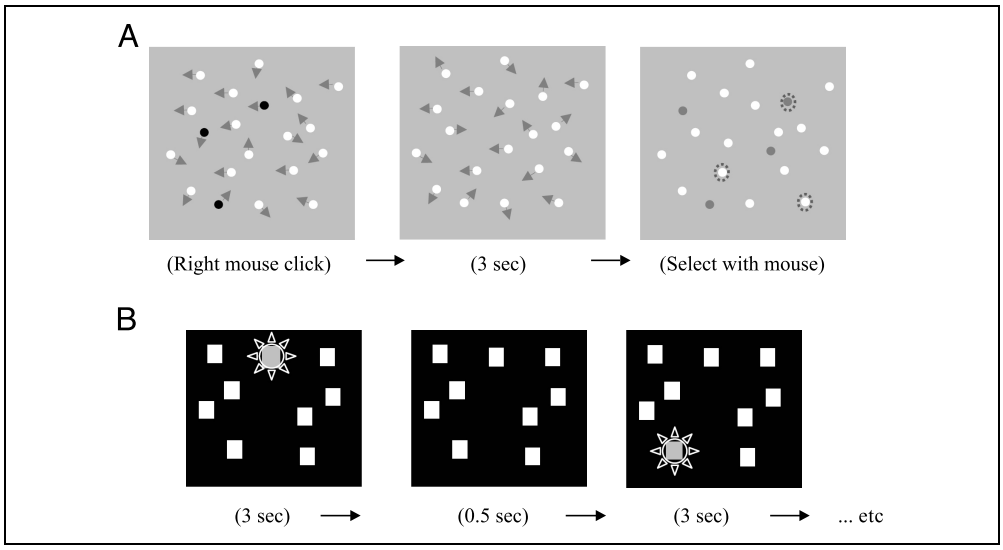

Figure 1. Experimental stimuli. (A) During multiple-object tracking, subjects were presented with 20 moving dots on a gray background, of which a subset (between 2 and 8) were identified as targets by a difference in color (shown in black). The trial was initiated by the subject clicking the right mouse key, after which the target dots became visually indistinguishable from the other dots. After a period of 3 sec, the dots became stationary and one of the original target dots (targets shown with outline) and three nontargets were colored orange (shown in gray). Subjects were then forced to choose which one of these four orange dots was the target. (B) The spatial working memory stimuli comprised nine white boxes placed randomly on a black background. A set number of boxes (between 2 and 9) were sequentially highlighted by a change in their color (shown in gray). The subject's task was to reproduce the sequence by touching the respective boxes in the correct order.

antagonist ketanserin would lead to a reduction in any psilocybin-related changes in attentional tracking or spatial working memory. This is particularly relevant given the recent work implicating the 5-HT_{2A} receptor in working memory function (Williams, Rao, & Goldman-Rakic, 2002).

RESULTS

Subjective Effects

The subjective effects of the four drug conditions, as measured by the 5D-ASC rating scale (Dittrich, Lamparter, & Maurer, 1999; Dittrich, 1998), are illustrated in Figure 2. The scores correspond to the five major factors: oceanic boundlessness (OB), anxious ego dissolution (AED), visionary restructuralization (VR), auditory alterations (AA), and reduced vigilance (RV). Significant main effects were found for drug [$F(3,21) = 18.15$, $p < .001$] and factor [$F(4,28) = 11.22$, $p < .001$] and a Treatment by Factor interaction [$F(12,84) = 14.51$, $p < .001$]. Tukey's post hoc analysis revealed that, compared to placebo, psilocybin caused a significant increase in four of the factors (OB: $p < .001$; AED: $p < .001$; VR: $p < .001$; RV: $p < .05$). After pretreatment with ketanserin, the subjective effects of psilocybin were largely blocked with only RV significantly effected ($p < .001$). Ketanserin alone had no significant subjective effects. Comparing the psilocybin-alone condition with the psilocybin after ketanserin pretreatment condition, no significant differences were observed for RV or AA, however, significant differences were seen for the other three factors (OB: $p < .001$; AED: $p < .05$; VR: $p < .001$).

Multiple-object Tracking

Performance on the tracking task varied inversely with the number of targets to track. It was close to perfect for two or three targets, but then dropped off markedly as the number of targets rose. To obtain a measure of task performance, we fitted the individual

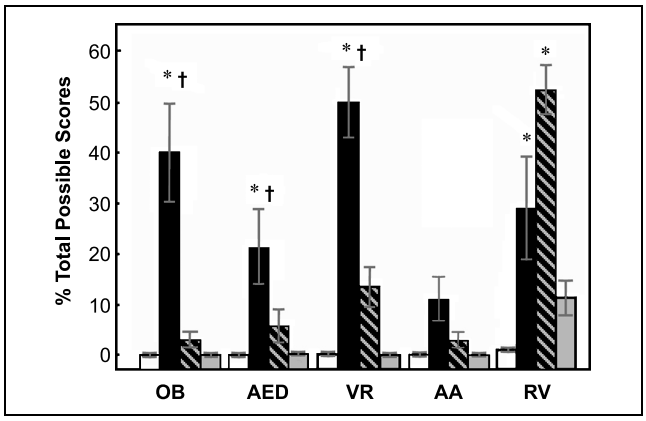

Figure 2. Results from the ASC questionnaire quantifying subjective effects experienced during placebo (white), psilocybin (black), psilocybin with ketanserin (black/gray stripes), and ketanserin alone (gray). The percentage of the total possible score relates to each of the five ASC main factors: oceanic boundlessness (OB), anxious ego dissolution (AED), visionary restructuralization (VR), auditory alterations (AA), and reduced vigilance (RV). Psilocybin caused significant changes, compared to placebo, in all factors except for AA. After pretreatment with ketanserin, the subjective effects of psilocybin were largely blocked with only RV remaining significantly elevated above placebo. Significant difference ($p < .05$) from placebo is denoted by "*," whereas differences between the psilocybin alone and psilocybin after pretreatment with ketanserin conditions are signalled by "†." The fine bars represent measures of standard error.

data with a simple model that assumed that subjects were capable of tracking a number of target items perfectly:

$$p(T) = \min\left(\frac{T_P}{T} + \frac{T - T_P}{rT}, 1\right)$$

where $p(T)$ is the proportion of correct responses for T number of targets, T_p is the number of targets that can be tracked perfectly and r is the number of response choices (equal to 4 in this study). The first term predicts the probability of correctly tracking a target; the second term allows for a correct guess, in the event that the target was not successfully tracked. Individual data were fitted with this function, minimizing squared errors to find the best value of T_p. In Figure 3A, the average data for each of the four conditions have been fitted by the model.

Using this same measure of performance calculated by the model (i.e., number of dots successfully tracked), a two-factor repeated-measures ANOVA found attentional tracking to be significantly affected by both drug [$F(3,21) = 3.38$, $p < .05$] and time [$F(1,7) = 18.06$, $p < .01$]. As would be expected, Tukey's post hoc analysis showed no significant difference between any of the four drug conditions at pretest. However, 120 min following drug administration, psilocybin ($\mu = 2.24$, $\sigma = 0.75$) and the psilocybin plus ketanserin pretreatment ($\mu = 2.35$, $\sigma = 0.60$) were both significantly ($p < .05$) reduced from placebo ($\mu = 3.15$, $\sigma = 0.57$) and ketanserin alone ($\mu = 3.14$, $\sigma = 0.69$), but did not differ significantly from each other ($p = .99$). Likewise, there was no difference between the placebo and ketanserin conditions ($p = .99$) (Figure 3B).

To ensure that the effects observed did not simply reflect the use of this particular model, the data were also analyzed in a more direct way. Similar to previous studies using this task, proportion of correct responses was considered for the five target dots, a condition in which response had neither saturated nor bottomed out. ANOVA showed attentional tracking to be significantly affected by drug administration [$F(3,21) = 3.64$, $p < .05$], with Tukey's post hoc analysis showing a significant reduction in performance from placebo and ketanserin, 120 min after drug intake, for both the psilocybin ($p < .01$) and psilocybin plus ketanserin ($p < .05$) conditions. Figure 3C shows results for the five target tracking as a discriminability index d' for the four different conditions, calculated from the percent correct scores, taking into account that it was a four-alternative forced-choice task.

Spatial Working Memory

Using a two-factor repeated-measures ANOVA, no significant effect on the number of boxes remembered correctly in sequence "span length" was found for drug [$F(3,21) = 0.57, p = 0.64$] or time [$F(1,7) = 1.56, p = .12$] (Figure 4A). Further confirming the lack of effect of psilocybin on spatial working memory performance, this nonsignificant result was similarly observed after a 2 × 2 ANOVA comparing only the placebo and psilocybin conditions, before and after drug intake [drug: $F(1,7) =$

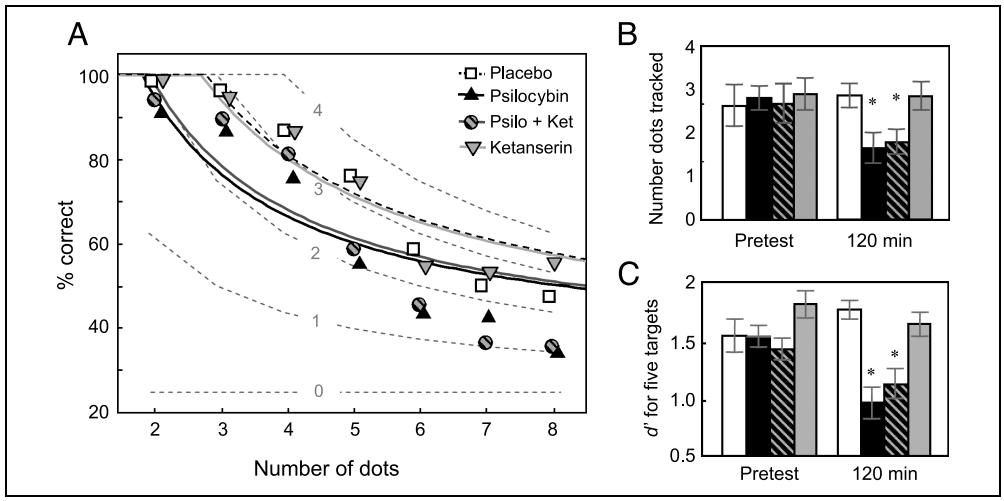

Figure 3. Psilocybin was found to significantly reduce attentional tracking performance and this effect was not diminished by pretreatment with ketanserin. (A) The mean percentage of correct responses across subjects for each number of target dots, 120 min postdrug administration, corresponding to the drug conditions: Placebo = white square (dashed line), psilocybin = black triangle (black line), psilocybin and ketanserin = striped circle (dark gray line), ketanserin = gray triangle (light gray line). The dashed gray lines indicate the percentage of correct responses predicted for subjects successfully tracking exactly 0 to 4 targets, respectively. (B) The calculated mean number of targets successfully tracked at pretest and 120 min under placebo (white), psilocybin (black), psilocybin with ketanserin (black/gray stripes), and ketanserin alone (gray). Psilocybin alone and in combination with ketanserin was significantly reduced from pretest and placebo levels 120 min after drug intake. There was no significant difference between any of the other time or drug conditions. (C) Discriminability index d' for trials with five tracking targets for the four different conditions (symbols as for B). Here d' was calculated from the percent correct scores, taking into account that it was a four-alternative forced-choice task. For both graphs, error bars represent standard errors of the mean, "*" denotes $p < .05$.

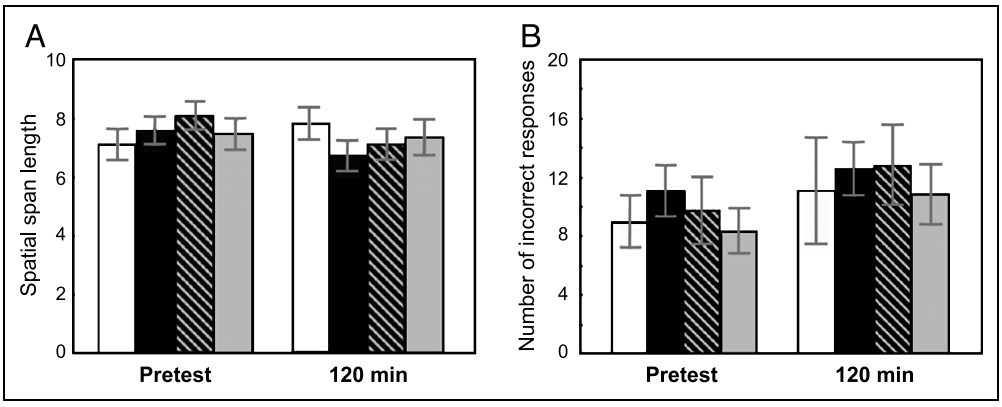

Figure 4. Spatial working memory was not significantly affected by the administration of psilocybin, or ketanserin. Placebo (white), psilocybin (black), psilocybin with ketanserin (black/gray stripes), and ketanserin alone (gray), at pretest and 120 min after drug administration. (A) Span length: The maximum number of boxes that were correctly recalled in sequence. (B) Total errors: The total number of incorrect boxes selected across all trials, including errors of box location or sequence order. Bars represent the mean and standard error.

0.61, p = .46; time: $F(1,7)$ = 0.06, p = .82]. The total number of errors in sequence order or location "total errors" was also unaffected by drug administration [$F(3,21)$ = 0.64, p = .60] or time of testing [$F(1,7)$ = 2.20, p = .18] (Figure 4B).

Individual Data

Figure 5 shows the individual results for the psilocybin and placebo condition as a scatter plot. The reduction in attentional tracking (ratio of pretest to 120-min peak testing) performance is plotted against the reduction in spatial working memory performance. Although there is some scatter in the data, most points show a greater effect for attentional tracking than spatial working memory. After psilocybin intake, there was virtually no correlation (r^2 = .01, p = .84) between the two measures, consistent with the claimed functional dissociation. This is compared to the placebo condition (r^2 = .25, p = .21—excluding the single outlier r^2 = .93, p = .004).

DISCUSSION

Administration of the subjectively hallucinogenic dose (215 μg/kg) of the 5-$HT_{1A/2A}$ agonist psilocybin was found to impair multiple-object tracking, but not spatial working memory. Pretreatment with the selective 5-HT_{2A} antagonist did not reduce this deficit. Psilocybin eliminated the correlation between performance on attentional tracking and spatial working memory tasks reported previously (Oksama & Hyona, 2004) and seen in the placebo condition of the current experiment. This finding suggests that psilocybin causes a selective attentional impairment and a resulting functional dissociation between attention and working memory processes. That this effect was not blocked by pretreatment with ketanserin implies that it may be mediated by activation of the 5-HT_{1A} rather than the 5-HT_{2A} receptor subtype. The observation that ketanserin alone had no effect on either the working memory or attentional tracking task is further evidence

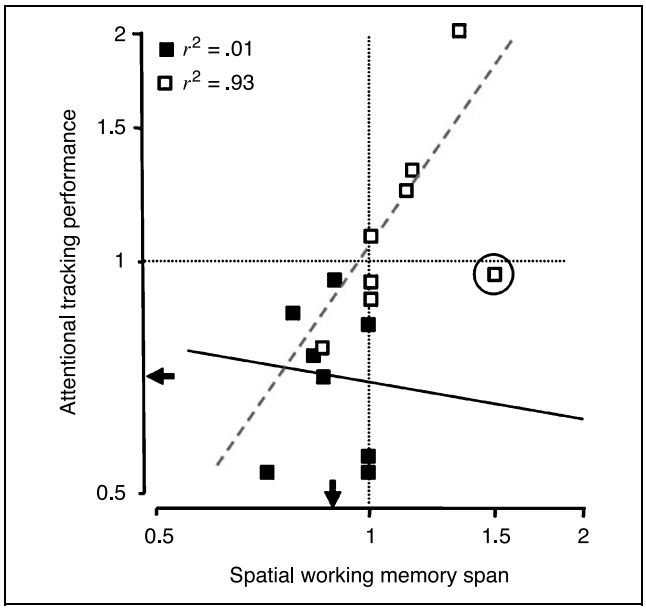

Figure 5. Individual data showing reduction in relative performance after psilocybin administration for attentional tracking (ordinate) plotted against spatial working memory (abscissa). The estimates of performance reduction were calculated as the ratio of pretest to the 120-min peak testing for the psilocybin condition. The respective symbols and regression line for the two conditions are: placebo = white square (dashed gray line) and psilocybin = black square (black line). The data point enclosed in a circle was treated as an outlier and not included in calculating the regression line. The arrows show the respective mean reduction in performance for the psilocybin condition. The vertical and horizontal dashed lines passing through unity correspond to no drug effect. The lack of correlation between the two tasks after psilocybin administration is further support that psilocybin leads to a functional dissociation between attentional tracking and spatial working memory.

against a direct role of the 5-HT_{2A} receptor in these processes.

Multiple-object Tracking

In order to calculate an overall measure of attentional performance, we fitted the data with a simple model based on the assumption that a correct response indicated either that the subject had successfully tracked the probe target or had correctly guessed its identity from the four response options provided. Comparing the calculated number of objects successfully tracked, psilocybin—both alone and after pretreatment with ketanserin—was found to significantly impair attentional tracking ability.

Data from previous human and animal studies suggest an involvement of serotonin (5-HT) and the 5-HT_{1A} receptor in attention (Winstanley et al., 2003; Rubinsztein et al., 2001; Carli & Samanin, 2000; Harrison et al., 1997). The results of the current study are consistent with the association between attentional impairments and reduced cortical 5-HT release implied in these studies, as psilocybin is known to inhibit 5-HT release via activation of presynaptic 5-HT_{1A} receptors in the raphe (Aghajanian & Hailgler, 1975). This interpretation is further supported by recent fMRI investigations that implicate regions of the frontal cortex in multiple-object tracking (Culham et al., 2001). Consequently, a psilocybin-induced reduction in the release of 5-HT into regions of the prefrontal cortex may disrupt multiple-object tracking ability, mediated by these regions.

The physiological mechanisms of attention are not yet well understood. However, it has been suggested that attention acts by modulating the magnitude rather than the selectivity of the response mediated by the respective neurons or cortical regions involved (Saenz, Buracas, & Boynton, 2002; Luck et al., 1997; Desimone & Duncan, 1995; Motter, 1994; Posner et al., 1980). This modulation is believed to be driven through bottom-up, mutual inhibition between lateral interactions and top-down feedback (Desimone, 1998; Desimone & Duncan, 1995; Luck et al., 1997). However, in addition to an enhancement of neural responses, more recent work has found that attention to a particular location also results in a widespread suppression of activity levels associated with nontarget objects (distracters) or visual field locations (Hopf, Boelmans, Schoenfeld, Heinze, & Luck, 2002; Chelazzi, Miller, Duncan, & Desimone, 2001; Smith, Singh, & Greenlee, 2000; Chelazzi, Duncan, Miller, & Desimone, 1998; Chelazzi, Miller, Duncan, & Desimone, 1993), such that ''cells responded as though the irrelevant distracters had been filtered from the visual field'' (Desimone, 1998). Here we speculate that the effects of psilocybin might reflect a relative reduction in the efficacy of these inhibitory processes.

The finding that ketanserin did not attenuate the observed attentional impairment suggests the 5-HT_{2A} receptor is not strongly involved in psilocybin's effects on attention. However, consideration of subjective reports suggests this conclusion may be overly simplistic. Subjects reported that after taking psilocybin, although they were still able to understand the task requirements, they generally found that the attention task was considerably harder. It was often reported that all of the dots became more dynamic, taking on ''a life of their own.'' One subject compared it to a bird's eye view of a Chinese market place, whereas another reported an impression of children chasing each other. This increase in salience of all of the dots may have made it more difficult both to selectively track the target dots and to ignore the ''distracter'' dots. After pretreatment with ketanserin, subjects verbally reported that they no longer experienced the increased intensity or ''personalities'' within the stimulus, but rather they reported a general feeling of sedation and associated difficulties with maintaining attention. These reports are in line with the results of the 5D-ASC self-rating scale that found psilocybin significantly affected each of the scale's five measures, and pretreatment with ketanserin returned most of these scores to baseline levels. The only 5D-ASC factor that remained significantly elevated was ''reduced vigilance,'' which relates to states of drowsiness, reduced alertness, and impairment of cognitive function. Therefore, although there was no difference in average performance between the psilocybin-alone condition and the psilocybin plus ketanserin condition, it cannot be ruled out that the two states were quite different, with the stimulation of the 5-HT_{1A} receptor leading to a reduction in vigilance and attentional performance, while the increased cortical stimulation associated with psilocybin induced activation of the 5-HT_{2A} receptor increasing the salience of the nontargets, making them harder to ignore. In support of this interpretation, performance under the psilocybin and psilocybin plus ketanserin conditions was found to be uncorrelated to the extent that there was even a slight but nonsignificant negative trend ($r = -.67$). However, much more data would be required before any conclusions could be drawn about independent mechanisms.

Spatial Working Memory

The current finding that a 215-μg/kg dose of psilocybin caused a slight but insignificant impairment of performance in spatial working memory is in line with a previous study that found performance on the same task to be completely unaffected by a lower dose of 115 μg/kg and slightly but significantly impaired with the higher dose of 250 μg/kg (Wittmann et al., submitted). This evidence that psilocybin has only minimal effects on spatial working memory was further corroborated by subjective reports that it was still possible to perform at the same level, but only that greater effort was required to remain focused on the task. This was even true at levels of

psilocybin that produced profound changes in conscious state. For example, one subject was convinced that the computer was trying to trick her, so she purposely reproduced the sequence incorrectly. On the following trials she decided that the computer ''had learnt its lesson'' and she made no subsequent errors. These results appear to stand in contradiction to experiments in monkeys and humans suggesting 5-HT_{2A} receptor involvement in spatial working memory (Williams et al., 2002; Vollenweider et al., 1998). However, neither of these studies reported direct changes in performance. In one study, an increase in response time on a spatial working memory task was interpreted as reflecting impaired spatial working memory function (Vollenweider et al., 1998). In the other study, 5-HT_{2A} stimulation enhanced spatial tuning and increased delay activity for preferred locations in a population of prefrontal neurons believed to be involved in working memory (Williams et al., 2002). Therefore, without clear evidence linking 5-HT_{2A} activation with changes in direct behavioral performance, the role of this receptor in spatial working memory remains unclear.

Attention and Working Memory

The functional dissociation that psilocybin produced between attentional tracking and spatial working memory goes against much of the current thinking that assumes considerable functional dependence between these two processes. The extent of this co-dependence has lead to attention being described as a ''gateway to memory'' wherein memory is believed to play a crucial role in determining which stimulus will be attended (Desimone, 1998). It was even suggested by Desimone (1998, p. 1252) that ''some of the neuronal mechanisms for memory and attention are so intertwined that one may question whether they are even distinguishable.'' Indeed, a considerable body of evidence links attention to working memory. Not only have they been shown to be functionally related (Oksama & Hyona, 2004), but the anatomical locations implicated in attentional tracking (Culham et al., 2001) are also believed to be involved in working memory (Courtney et al., 1998; Courtney, Ungerleider, Keil, & Haxby, 1997). However, the results of the current study suggest that it might be possible to tease the two processes apart. This co-dependence may be limited to only certain elements of the two processes. For example, if attentional tracking and working memory both involve (1) selection of targets, (2) biasing the selected targets relative to distracters, and (3) maintenance of the state over time, it may be the case that psilocybin is selectively disrupting only this second stage. One clear prediction based on this speculation is that performance on attentional tasks without distracting components would be unaffected or even enhanced by psilocybin, whereas spatial working memory tasks involving some distracting elements would be more strongly impaired.

Although the above interpretation is in line with the observed results, it should be considered with caution at this stage. One difficulty is that, despite the clear selectivity in impairment observed here, the current study cannot rule out the possibility that the results reflect a difference in sensitivity of the two tasks. Although the responses were not saturated in either task, there is a possibility that difficulty was not well matched to the attentional task, accounting for the difference in observed results. Confirmation of the reported functional dissociation, therefore, will depend on future experiments more comprehensively comparing performance between the two tasks. In addition, the sample for this study was small: only eight subjects were tested, of which five reported previous exposure to psilocybin. There is no reason to expect that prior psilocybin use would have affected performance on the task, however, this possibility cannot be ruled out without consideration of a larger sample size allowing for a comparison between psilocybin-naïve subjects and those with prior experience.

Impulsivity and Psychosis

One final area warranting further investigation is the effect of psilocybin on impulsivity. There is considerable evidence connecting the serotonergic system to impulsivity (Carli & Samanin, 2000; Soubrié, 1986; Linnoila et al., 1983). Although we did not specifically measure response times in this study, it seems unlikely that the performance deficit observed reflected errors resulting directly from response impulsivity, as both measures would be expected to be equally susceptible to premature response errors and because response times are consistently increased by psilocybin (Carter et al., 2005; Gouzoulis-Mayfrank et al., 2002; Vollenweider et al., 1998). However, it is possible that the attentional deficits observed here are related to more complex characteristics of impulsivity generally associated with measures of attention such as decreased latent inhibition (an animal's capacity to ignore stimuli that experience has shown are irrelevant to its needs) (Lorden, Rickert, & Berry, 1983), behavioral/response inhibition (Carli & Samanin, 2000; Harrison et al., 1997), and distractibility (Oades, Slusarek, Velling, & Bondy, 2002).

In addition to impulsivity, the results are also relevant to current models of psychosis and the development of related pharmacological therapies. Psilocybin has previously been considered as a transient ''model'' form of psychosis (Vollenweider & Geyer, 2001). Not only is there evidence of some overlap in the symptomatology between the psilocybin state and psychotic episodes, but it is also the case that a number of antipsychotic medications target the same 5-HT receptors activated by psilocybin (for review, see Roth, Hanizavareh, & Blum,

2004). Generalized cognitive and attentional deficits are common symptoms in a number of clinical conditions such as obsessive–compulsive disorder (Clayton et al., 1999; Martinot et al., 1990), autism (Sturm et al., 2004), attention deficit disorder (Barkley, 1997), and schizophrenia (Addington & Addington, 1998; Nuechterlein & Dawson, 1984). Therefore, a better understanding of the pharmacology underlying these attentional processes may offer new insight for potential drug therapies.

Conclusion

A variety of evidence suggests that attention, working memory, and serotonin are functionally and anatomically intertwined. The finding that a moderate dose of the 5-$HT_{1A/2A}$ agonist psilocybin selectively impairs attentional tracking but not spatial working memory performance offers an initial attempt to tease these elements apart. Further work is still needed to investigate the proposition that the key effect of psilocybin on attention is a weakening of the capacity to filter out irrelevant stimuli, leading to increases in distractibility and reduced inhibition.

METHODS

Subjects

Eight healthy volunteers (5 men, 3 women) aged between 21 and 31 (mean = 27.0, *SD* = 2.7) were recruited through advertisement from the local university and technical college. After being informed by a written and oral description of the aim, procedures, and possible risks associated with the study, 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 of good physical health as assessed by 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 disorders or 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 three were psilocybin-naïve. Subjects were reimbursed for their time and they were informed that at any time they were free to withdraw from the study.

Substance and Dosing

Psilocybin was obtained through the Swiss Federal Office of Public Health. Capsules of psilocybin (1 and 5 mg) and ketanserin (50 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), ketanserin (50 mg), and lactose placebo were administered in gelatin capsules of identical appearance. The doses of psilocybin and ketanserin used in the present study were chosen because they had previously been shown to induce and block the associated changes in conscious state, respectively (Vollenweider et al., 1998). In order to ensure occupancy of the 5-HT_{2A} receptor, ketanserin was administered 90 min prior to psilocybin.

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

Stimulus and Procedures

Attention—Multiple-object Tracking

Subjects viewed a Sony Trinitron Multiscan E215 monitor (44 cm) from a distance of approximately 60 cm. Twenty disks (1° diameter) moved across the gray screen in Brownian-like motion, at a constant speed of 6°/sec. Every 30 msec the trajectory of all dots changed independently by an angle drawn at random from a Gaussian distribution with standard deviation of 11°. When the dots collided, they appeared to bounce off each other or with the edges of the screen.

At the beginning of each trial, the ''distracter'' (irrelevant) dots were colored green and the ''target'' dots (those to be tracked) were colored red. Subjects initiated a trial by pressing a mouse key, causing the red disks to become green and continue their random walk for 3 sec. They then all stopped, and four dots—one target and three distracters—were highlighted orange. The subject indicated which of the four dots had been a target using the mouse cursor. A feedback tone indicated an incorrect response. In each block of trials, the target number was initially set at 2, increasing gradually up to 8, with 4 repetitions for each target number. Three blocks were run in each testing session, yielding a total of 84 trials.

There was no fixation marker and although subjects were not explicitly required to maintain fixation, they were instructed to track the targets with their attention rather than their eyes. The stimulus was generated in Matlab, using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997).

Spatial Working Memory

Spatial working memory was assessed using the Spatial Span test taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB). The Spatial Span test is a computerized version of Corsi's block tapping task (Milner, 1971) designed to measure spatial working memory span (Robbins et al., 1994; Sahakian & Owen,

1992). For this test, nine white boxes (3 cm^2) arranged irregularly on a black background were presented on an Ilyama S500M1 monitor with an Elo IntelliTouch Touchscreen and internal serial controller. During each trial, a set number of the boxes were sequentially highlighted by a change in their color. Each box was highlighted for the duration of 3 sec and the period between each subsequent box highlighting was 0.5 sec (during which time all boxes were white). The color used was consistent within any trial but was alternated between trials.

The subject was instructed to remember the order in which the boxes were highlighted and then reproduce it at the end of the trial by touching the boxes in the appropriate sequence. Subjects were initially presented with a sequence of two boxes, after this the trials became successively harder with one additional box being added after every correct response sequence (up to 9 boxes). In the case of an incorrect response, the following trial would repeat the same number of boxes. The test was terminated after three incorrect responses at the respective level. Each trial was initiated by the subject pressing the space bar and at the end of the trial the subject's response was cued by a beep. There was no maximum limit on response time, but a minimum limit of 1 sec between successive responses in the sequences was imposed. During the response sequence, each selected box was highlighted in the same color that had been used during the test sequence and a feedback tone was generated.

As subjects were required to repeat the Spatial Span task a number of times over the 4 days of testing, four parallel versions of the test were used to reduce the possibility of the sequences becoming encoded in long-term memory. The four versions differed only in the sequence and color in which the boxes were highlighted. The order in which the parallel tests were presented was counterbalanced across the eight subjects and the four drug conditions.

Psychological Ratings

The Altered State of Consciousness (5D-ASC) rating scale (Dittrich et al., 1999; Dittrich, 1998) was used to assess the subjective effects under the four drug conditions as it had previously been shown to be sensitive to psychological effects of psilocybin in humans (Hasler et al., 2004; Vollenweider et al., 1998;Vollenweider et al., 1997). 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.
2. ''Anxious ego dissolution'' (AED) measures ego-disintegration associated with loss of self-control, disordered thought, arousal, and anxiety.
3. ''Visionary restructuralization'' (VR) including elementary and complex hallucinations, synesthesia, and changed meaning of percepts.
4. ''Auditory alterations'' (AA) refers to acoustic hallucinations and distortions in auditory experiences.
5. ''Reduction of vigilance'' (RV) relates to states of drowsiness, reduced alertness, and impairment of cognitive function.

Experimental Design

The study was double-blind, placebo-controlled, with the order of dose assignment counterbalanced, and each of the four experimental days separated by at least 14 days. Before participating in either of the experimental conditions, subjects were taken through each of the measures to ensure that they were familiar and comfortable with all tests upon arrival for their first experimental day. For each of the four experiment days, subjects were instructed to have a light breakfast prior to arrival at the hospital. Before testing began, blood pressure and heart rate were measured and subsequently monitored at hourly intervals throughout the day. To obtain baseline ''pretest'' scores, subjects were tested on both the attentional tracking and working memory tasks. Following pretesting, the ketanserin/placebo capsules were ingested, and after a further 90 min, the placebo/psilocybin capsules were administered. To minimize anxiety, subjects were then advised to relax and allow themselves to become comfortable with any perceptual or cognitive changes experienced. Because plasma levels of psilocybin's active metabolite psilocin peak approximately 105 ± 37 min after drug intake (Hasler et al., 1997), subjects were retested on the tracking and working memory task 120 min after administration of psilocybin. The order of testing for the two tasks was sequentially alternated and counterbalanced. Subjects completed the 5D-ASC rating scale 180 min after drug administration and were thereby instructed to rate their experience since psilocybin intake (0–180 min).

At pretest, 90–120 min postdrug intake and at a selection of additional intervals throughout the day, a number of other psychometric and psychophysical

measures were administered but the results will be presented separately (Carter et al., submitted). Subjects finished participation in the study approximately 7 hr after psilocybin consumption and were examined by the principal investigator before being deemed fit to be released.

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