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ORIGINAL INVESTIGATION

A long-term ecstasy-related change in visual perception

John Brown · Mark Edwards · Elinor McKone · Jeff Ward

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Abstract
Rationale The present study provides the first evidence of the long-term consequences of ecstasy use on visual processes thought to reflect serotonergic functions in the occipital lobe. Methylenedioxymethamphetamine ("ecstasy") is known to cause lasting changes to the serotonin system in animals, and convergent evidence suggests that similar changes occur in human ecstasy users. Other research suggests that serotonin may be involved in lateral inhibition between orientation sensitive neurons in the occipital lobe, and that disruption to the serotonin system causes an increase in the magnitude of the tilt aftereffect illusion that is known depend on those neurons.
Objectives The aim of the present study was to determine if ecstasy users have detectable changes in occipital lobe behavioural functioning, as revealed by the tilt aftereffect illusion.
Materials and methods Thirty ecstasy users and 34 non-drug using controls were compared on the magnitude of the tilt aftereffect illusion following adaptation to stimuli oriented at 15 and 40° from vertical.
Results Ecstasy users who had not used amphetamines for 115 days or more had a larger average tilt aftereffect than non-drug using controls after adaptation to 40° stimuli but not after adaptation to 15° stimuli. Additionally, there was no difference between non-drug using controls and ecstasy users who had used amphetamines within the last 61 days at either adaptation angle.
Conclusions The results were consistent with the proposal that ecstasy-related damage to the serotonin system causes behavioural changes on tests of visual perception processes that are thought to reflect serotonergic functions in the occipital lobe.

Keywords MDMA · Ecstasy · Amphetamine · Methamphetamine · Visual perception · Occipital lobe · Orientation · Tilt aftereffect · Serotonin · Lateral inhibition

J. Brown (✉) · M. Edwards · E. McKone · J. Ward
School of Psychology, The Australian National University, Building 39,
Canberra 0200, Australia
e-mail: john.brown@anu.edu.au

"Ecstasy" is a popular recreational drug in many parts of the world. A growing body of evidence suggests that the main psychoactive ingredient of ecstasy, methylenedioxymethamphetamine (MDMA), causes irreparable harm to the neurology and cognitive functioning of the brain. MDMA has been described as a synthetic ring-substituted phenethylamine that is structurally related to both amphetamine-like stimulants and mescaline-like hallucinogens (Fantegrossi et al. 2002). MDMA and other related 3,4-methylendioxy-substituted amphetamines, such as MDA and MDEA, produce feelings of euphoria and social closeness (Nichols and Oberlender 1990; Shulgin 1990; Steele et al. 1994).

Animal studies indicate that MDMA can cause lasting changes to the functioning of serotonergic axons and serotonin availability in the brains of animals, including higher primates (for review, see Green et al. 2003; Wang et al. 2004). There is also an increasing body of convergent evidence that recreational ecstasy use is sufficient to cause equivalent changes in humans (for review, see Green et al. 2003, also Buchert et al. 2003, 2004; Daumann et al. 2004; de Win et al. 2004; McCann et al. 2005). In addition to neural changes, ecstasy use has also been shown to be associated with lasting changes in long-term memory, mood, aggression, somatic complaints, psychopathology

and executive functioning (e.g. Daumann et al. 2003; Fox et al. 2001; Gerra et al. 2001; Hanson and Luciana 2004; Thomasius et al. 2003), although such findings have not been universally reported (e.g. Cole et al. 2002; Croft et al. 2001; Dafters et al. 1999; Klugman et al. 1999).

The present article investigates possible ecstasy-related long-term effects on visual processes that are thought to rely on serotonergic neural activity in the occipital lobe. Some studies have reported changes in the neural functioning of the occipital lobes of ecstasy users, as revealed by electroencephalogram and functional magnetic resonance imaging (fMRI) measurements (e.g. Cowan et al. 2006; Daumann et al. 2003; Gamma et al. 2000). However, there have been no studies published to date that have investigated if these changes result in alterations in the behavioural functioning of ecstasy users, as indicated by performance differences between ecstasy users and controls on tasks that are thought to reflect occipital lobe processes.

The occipital lobe contains the primary visual processing area of the brain, commonly designated as "V1" (Wilson and Cragg 1967). Area V1 receives input from the eyes via sub-cortical brain structures and projects outputs to other parts of the visual cortex along various neural pathways (Engel et al. 1994; Heimer 1994; Hubel and Wiesel 1974). As visual information is transferred along these pathways, the type of information represented by the activation of neurons in each area increases in complexity. Information that is directly processed in V1 is limited to basic visual attributes like the detection of the orientation of lines and edges, as well as simple motion and stereoscopic depth information (Hubel and Wiesel 1970; Zeki 1978).

Orientation processing is a primary function of area V1. This is evidenced by the highly organised columnar arrangement of neurons in V1, such that neurons within each column are tuned to detect lines of a particular orientation within a specific region of the visual field, and neurons in neighbouring columns respond to slightly different orientations within the same part of the visual field (Hubel and Wiesel 1974; Tootell et al. 1998). The level of activation of these neurons decreases significantly for lines angled away from the orientation to which it is tuned (for the 'preferred' orientation of that neuron, see Fig. 1). The range of orientations that a particular neuron responds to is called its bandwidth, often represented by the width of the tuning curve at half of the maximum height of the curve. Single-cell recording experiments in primates have shown that the tuning bandwidth for most individual neurons is between 20 and 50° (Ringach et al. 2002; Schiller et al. 1976). As a consequence, a line of any given orientation in a particular receptive field is represented at a neural level by the activation of a large number of neurons tuned to a wide range of orientations (the population response). Each neuron in the population response has a

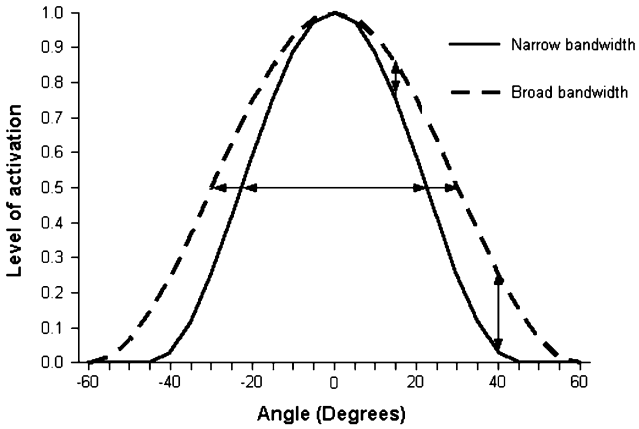

Fig. 1 Example tuning-curves for two orientation-sensitive neurons in the occipital lobe, one with a relatively narrow bandwidth and the other with a relatively broad bandwidth . The sample neurons shown both respond with the maximum level of activation for *vertical lines* (i.e. their preferred orientation). The narrow bandwidth neuron has a bandwidth of approximately 45° as determined at the width of the curve at half the height of the curve, whereas the other neuron has a bandwidth of approximately 60°. The *vertical arrows* highlight that the difference in activation between the neurons is much greater for stimuli 40° from the preferred orientation than for stimuli at 15° from the preferred orientation

level of activation inversely proportional to the difference between its preferred orientation and the orientation of the stimulus. Broader tuning bandwidths result in more neurons being at least partially activated by a given stimulus. Hence, the broader the bandwidth of individual neurons, the greater the range of preferred orientations represented in the population response.

The bandwidth of V1 neurons is determined in part by lateral inhibition between neurons. When an orientation-sensitive neuron is activated, it sends signals to inhibit the level of activation of neurons tuned to nearby orientations (Shapley et al. 2003). This serves to decrease the level of activation of each neuron to orientations apart from the preferred orientation it is tuned to thereby narrowing the tuning curve bandwidth of each neuron. Note that while lateral inhibition affects the bandwidth of the tuning curve, it does not alter the maximum level of activation of the neurons when stimulated by their preferred orientation.

Of particular interest to the present study is evidence that serotonin may be involved in the normal operation of orientation-sensitive neurons. This is revealed by the effect of serotonin depletion caused by tryptophan depletion on the *tilt aftereffect* illusion (Masini et al. 1990). The tilt aftereffect is a visual illusion that can be easily observed by staring at a set of parallel lines angled at, say, 15° to the right of vertical (the 'adaptation angle') for a few minutes (adaptation phase), then looking at a set of vertical lines (test phase; see Fig. 2). Under these conditions, the vertical lines at test appear to be orientated slightly to the *left* of vertical. Thus, the tilt aftereffect is observed as a deflection of the orientation of the test stimulus away from the

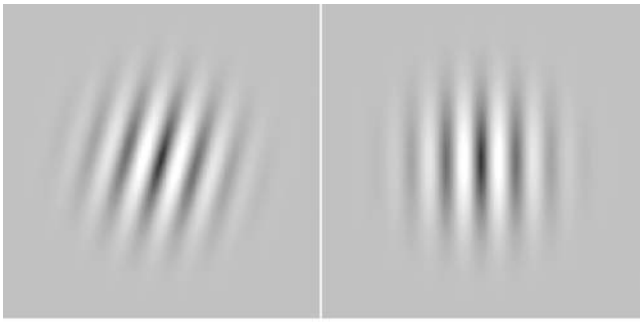

Fig. 2 Example Gabor stimuli at various orientations. The tilt aftereffect can be observed by slowly scanning **a** for 90 s, after which **b**—which is in fact vertical—should appear orientated slightly to the *left* of vertical

orientation of an adaptation stimulus. The magnitude of the tilt aftereffect is defined as the difference between the angle perceived as vertical before adaptation and the angle perceived as vertical after adaptation. The maximum tilt aftereffect occurs for adaptation angles between 10 and 20° from vertical and is reached with an adaptation time of as little as 90 s (Gibson and Radner 1937).

The tilt aftereffect illusion is thought to principally result from a reduction in the sensitivity of V1 neurons after prolonged exposure to a stimulus that they are tuned to respond to (Carpenter and Blakemore 1973; as distinct from the process of lateral inhibition outlined earlier involved in moderating the bandwidth of tuning curves). At the onset of the adapting stimulus, the neurons, which are tuned to the orientation of the stimulus, will be highly activated. Other neurons that are optimally tuned to nearby orientations will be partially activated, provided that their tuning bandwidth includes the adaptation orientation. During the adaptation phase, the protracted activation of affected neurons results in a decrease in the sensitivity of those neurons to changes in the stimulus by an amount proportional to their initial activation level. This lowered level of sensitivity persists after the adaptation stimulus is removed, only gradually returning to pre-adaptation levels. As a consequence, when a vertical post-adaptation stimulus is presented, those neurons that have undergone adaptation are unable to respond to the level they would have otherwise achieved. This results in a skewed population response, which is very similar to that which would have been produced by a pre-adaptation stimulus orientated slightly in the opposite direction to that of the adaptation stimulus. Therefore, the percept is one of the lines tilted in that direction.

Masini et al. (1990) compared the magnitude of the tilt aftereffect before and after participants had been treated with a tryptophan depletion diet. Tryptophan is critically involved in the regulation of serotonin synthesis in the brain, and the tryptophan depletion technique has been shown to lower plasma tryptophan level by 80–90% within 5–7 h of ingestion (Bell et al. 2001). In animal studies, this has been shown to result in a corresponding reduction in serotonin synthesis and release in the central nervous system (Gartside et al. 1992). Masini et al. (1990) found that tryptophan depletion was associated with a statistically significant *increase* in the magnitude of the tilt aftereffect, such that in the control, condition lines at 0.43° were perceived as being vertical after adaptation, whereas in the tryptophan depletion, condition lines at 1.07° were perceived as being vertical after adaptation. This suggests that serotonin is involved in moderating the magnitude of the tilt aftereffect.

Masini et al. (1990) interpreted their finding as being consistent with the critical involvement of serotonin in lateral inhibition. If serotonin is involved in lateral inhibition as proposed, then serotonin depletion would result in less lateral inhibition, which in turn would increase the tuning bandwidth of affected neurons, thus increasing the range of preferred orientations represented in the population response. Consequently, the range of neurons that would undergo adaptation would also increase. This would in turn increase the size of the distortion in the perceived orientation of the test stimulus and thereby increase the magnitude of the tilt aftereffect.

The present study investigated whether or not the long-term disruption to the serotonin system caused by recreational MDMA/ecstasy use would result in a similar increase in the magnitude of the tilt aftereffect to that caused by the tryptophan depletion of serotonin in Masini et al. (1990). Towards this goal, the tilt aftereffect in ecstasy users was compared to that in non-drug using controls. It was expected that the magnitude of the tilt aftereffect after a 15° adaptation stimulus might be greater in ecstasy users compared to non-drug users.

In addition to the 15° adaptation angle tested by Masini et al. (1990), an important addition in the present study was the inclusion of a 40° adaptation condition. The 40° condition was tested to obtain further data regarding whether differences in the tilt aftereffect of ecstasy users are mediated by decreased lateral inhibition between V1 neurons. In non-drug studies, the maximum tilt aftereffect is obtained for adaptation angles of 10–20° away from vertical. For angles greater than 20° and up to 45–55°, the magnitude of the tilt aftereffect gradually reduces to zero. At a neural level, this is thought to occur because, as the adaptation angle is increased, the overlap between the population response to the adaptation stimulus and the population response to the test stimulus is decreased thereby decreasing the size of the aftereffect.

If the tuning bandwidth of the neurons is increased by ecstasy-related damage to the serotonin system, then the difference between the shape of the tuning curves between orientation sensitive neurons of ecstasy users and controls

would be similar to the difference between the tuning curves of the broad and narrow bandwidth neurons, respectively, as illustrated in Fig. 1. Because lateral inhibition is thought to affect the tuning bandwidth of neurons, but not the maximum level of activation, the level of activation at the preferred orientation (i.e. at 0° for the example neurons in Fig. 1) would be expected to be the same for ecstasy users and controls. However, for angles away from the preferred orientation, the expected wider bandwidth of V1 neurons in ecstasy users would result in a greater *change* in the level of activation of neurons with preferred orientations at large angles away from the stimulus (e.g. 40°) than neurons with preferred orientations at 15° to the stimulus, as illustrated in Fig. 1. Thus, the *difference* in the magnitude of the tilt aftereffect between ecstasy users and controls should be greater for an adaptation angle of 40° than at 15°, although the magnitude of the tilt aftereffect at 40° would still be much *lower* than that at 15° for both ecstasy users and controls.

In the present study, the magnitude of the tilt aftereffect was measured using the method of constant stimuli (described in Gescheider 1985). This involved brief presentations (100 ms) of the test stimulus over a set of test angles. For each presentation, participants made a two-alternative forced-choice response to indicate if the test stimulus appeared to be oriented to the left or the right of vertical. The proportion of 'oriented to the right' responses at each test angle was calculated for each participant, and a psychometric (sigmoid) curve fitted to the data. From this, the point on the psychometric curve at which the proportion of 'left' and 'right' responses was 0.5 (i.e., 50%) was determined. This point is called the 'point of subjective equality' (PSE), because at that test angle, the stimulus would appear to the participant to be angled equally between left and right (i.e. vertical). This testing procedure was conducted before and after adaptation, and the shift in the PSE (post-adaptation minus pre-adaptation) was taken as the magnitude of the tilt aftereffect for that adaptation angle.

The method used in the present study also allowed the calculation of the slope of the psychometric curve at the PSE of sigmoid function. The slope of the psychometric curve provides an indication of participants' ability to discriminate between different orientations, as revealed by the difference in orientation of the test stimulus required to discriminate just-noticeably-left orientations from those that are just-noticeably-right. Evidence for a relationship between serotonin and discriminability has been found in a study on rats. Asgari et al. (2005) found that interrupting the operation of the serotonin system using a serotonin agonist resulted in both an increase in the average PSE and a decrease in the average slope of the psychometric curves on a temporal discrimination task. It is possible that ecstasy-related disruption to the serotonin system may result in a similar effect on the slopes for the responses of ecstasy users engaged in the visual task in the present study. Such a finding would again be consistent with an increase in the tuning bandwidth of orientation sensitive neurons.

Materials and methods

Participants

Participants were recruited in 2004 from Canberra, Australia, using the respondent-driven "snowball" sampling technique (Wang et al. 2005). All persons gave their informed consent before their inclusion in the study. The study was approved by the Australian National University Human Research Ethics Committee and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. A drug use history was obtained for each participant using a time-line interview (based on Anglin et al. 1993). The participants were also assessed on demographic, estimated IQ, mental health and personality variables to evaluate the extent to which those variables could account for any differences observed between the groups on the tilt aftereffect. Demographic variables were age, sex and highest level of education attained. Estimated IQ was calculated from the number of reading errors on the Contextual AusNART using a formula developed on a sample of 18- to 34-year-old Australians, where estimated (full scale) IQ=117.33−(0.69×E) where E = the number of errors (Lucas et al. 2003). Mental health was assessed using the brief symptom inventory (BSI, Derogatis 1993). Personality was assessed using the sensation seeking scale (SSS, Zuckerman 1994). Sensation seeking was selected as the most relevant personality variable because it has been shown to be a consistent predictor of drug use and to have a strong heritable component (see Section 2.4.3.3, Dughiero et al. 2001; Zuckerman 1994).

Sixty-four people were consigned to either an ecstasy users group or non-drug using control group on the basis of their drug use history. Table 1 provides a summary of the characteristics of the ecstasy users and non-drug using controls. Importantly, the groups were closely matched on most demographic variables, with the exception that ecstasy users had a slightly lower estimated IQ than non-drug using controls. Ecstasy users had also consumed considerably more alcohol in higher maximum doses than non-drug using controls and had higher scores on some personality variables (the experience seeking and disinhibition indexes of the SSS, as expected), as well as some mental health measures (the somatisation and obsessive-compulsive subscales of the BSI). The potential influence of these variables on the outcomes of the study were controlled for by

Table 1 Characteristics of ecstasy users and controls in the visual perception study

	Controls (n=34)	Ecstasy (n=30)	p Values
Sex (male %)	65%	63%	.ns
	Mean (SEM)	Mean (SEM)	
Age (years)	23.24 (0.69)	23.23 (0.68)	.ns
Highest level of education attained[a]	3.35 (0.09)	3.23 (0.10)	.ns
Estimated IQ	107.35 (0.82)	104.15 (0.95)	0.01
Ecstasy			
Lifetime dose (tablets)	–	394.54 (123.01)	
Abstinence (days)	–	55.81 (15.94)	
Alcohol			
Lifetime dose (standard drinks)	1,023 (226)	4,846 (771)	<0.001
Maximum monthly dose	27.0 (5.9)	122.4 (17.5)	<0.001
Maximum ever dose	14.2 (1.54)	20.9 (1.40)	0.002
Sensation-seeking scale			
Experience seeking	5.53 (0.31)	7.90 (0.23)	<0.001
Disinhibition	4.74 (0.37)	6.87 (0.35)	<0.001
Brief symptom inventory			
Somatization	47.21 (1.10)	51.60 (1.72)	0.04
Obsessive compulsive	56.29 (1.37)	61.03 (1.73)	0.03

.ns indicates p>0.05

SEM Standard error of the mean

[a] 1=Year 10 (middle secondary education); 2=Year 12 (upper secondary education); 3=bachelor undergraduate degree; 4=post-graduate degree

statistical means. Some incidental use of cannabis was tolerated in the control group because of the difficulty in finding people who had never tried cannabis (for this sub-group: n=11, lifetime dose: mean=2.9 times, SD=2.67 and range=1–9 times. Last use: mean=1,591 days before testing, SD=1,650 and range=127–6,125 days).

Design

The effect of ecstasy use on the behavioural sensitivity to orientation was examined by comparing ecstasy users and non-drug using controls on the magnitude of the tilt aftereffect. Adaptation angle (15°, 40° to the right of vertical) was manipulated within-subjects.

Stimuli and equipment

The stimulus consisted of a Gabor, which is a sinusoidal variation of luminance level within a Gaussian window (Fig. 2a; size 9° of visual angle, standard deviation 1.3°, spatial frequency 1 cycle/degrees, 100% contrast) displayed on a uniform luminance screen of 100 Cd/m^2, created using a Cambridge Research Systems VSG 2/5 graphics card (resolution 1,312×983 pixels at a refresh rate of 80 Hz), which was displayed in the centre of a Clinton Monoray monitor. The participants sat with their head on a chin rest approximately 50 cm from the screen, such that their eyes were level with the centre of the monitor. An adjustable curved-forehead rest was used to restrict head tilt. Testing was conducted in a dimly lit room after several minutes of dim-light adaptation, with featureless black walls and computer equipment shrouded in black cloth.

Procedure

For each adaptation angle, the experiment included three phases, namely, the pre-adaptation test, the adaptation phase and the post-adaptation test. For the pre-adaptation tests, a Gabor was displayed for 100 ms at an orientation randomly selected without replacement from a range of nine possible test angles: −2.8, −2.1, −1.4, −0.7, 0, +0.7, +1.4, +2.1 and +2.8 degrees from vertical, where negative angles were to the left of vertical and positive angles were to the right. The participants indicated if they thought the lines in the Gabor had been sloped to the left or the right using two keys on the keyboard. If they failed to respond within 3 s, a beep sounded, and the trial was re-inserted into the remaining set. The next trial commenced after a 500-ms delay. This was repeated until the participant had responded to all of the test angles once. The entire set of test angles was then repeated until the participant had responded to each test angle ten times, making a total of 90 responses.

The participants were then adapted to a Gabor displayed at an adaptation angle of either 15 or 40° for 90 s. They were specifically instructed to *not* maintain a fixed gaze on the centre of the stimulus. Instead, they were to slowly scan the stimulus to avoid generating afterimages, while keeping the stimulus in focus at all times. The start of the adaptation phase was indicated by the word “study” flashing on the screen for 1 s outside the visible perimeter of the adaptation Gabor. To avoid cueing the orientation of true vertical, the word was orientated perpendicular to the lines of the Gabor and positioned just beyond the end of the longest line of the Gabor.

The post-adaptation test was the same as the pre-adaptation test, except that a 10-s “top up” adaptation was given after every fifth trial, and additional test angles were used (+3.5, +4.2, +4.9, +5.6, +6.3 and +7.0°) in addition to the nine used in the pre-adaptation test, making a total of 15 test angles. Pilot testing revealed that the additional post-adaptation test angles were necessary to ensure adequate data for the fitting of a psychometric curve after the adaptation had shifted the curve to the right.

After testing was completed for one adaptation angle, there was a filled delay of approximately 10 min (during which the participants completed a verbal memory test conducted for a separate study) before all three phases were repeated for the remaining adaptation angle (the order of the 15 and 40° adaptation angles was counterbalanced across participants). The filled delay was incorporated to avoid any carryover of adaptation between the tests.

Before commencement of the first pre-adaptation test, participants were given between one and three sets of nine practice trials of the post-adaptation test procedure to familiarise them with the display and to ensure they could correctly use the response keys. For the 10-s-up adaptation in the practice trials, a vertically orientated Gabor (Fig. 2b) was used to avoid unwanted adaptation.

Results

Cohort effects on the magnitude of the tilt aftereffect

The tilt aftereffect data consisted of the proportion of 'orientated-to-the-right' key responses made by participants for each test angle in the pre- and post-adaptation tests for each adaptation angle (15° pre-adaptation, 15° post-adaptation, 40° pre-adaptation and 40° post-adaptation). A separate psychometric curve was fitted to the data of each participant in each condition, and the PSE of each curve—the orientation of the stimulus that the participant perceived as upright—was calculated. The magnitude of the tilt aftereffect at each adaptation angle was taken as the PSE of the post-adaptation curve minus the PSE of the associated pre-adaptation curve, such that a positive number would indicate an adaptation aftereffect in the expected direction. The mean for each cohort was then calculated as a function of adaptation angle. The average magnitude of the tilt-aftereffect after adaptation to 15° was 2.82° (SE=0.58°, n=34) for non-drug using controls and 2.75° (SE=0.70°, n=30) for ecstasy users. After adaptation to 40°, the average magnitude of the tilt-aftereffect was 1.43° (SE=0.67) for non-drug using controls and 1.58° (SE=0.50°) for ecstasy users.

A mixed model analysis of variance (ANOVA) was conducted on the magnitude of the tilt aftereffect as a function of adaptation angle (15 and 40°) and cohort (ecstasy users, non-drug using controls). This revealed that the main effect of adaptation angle was statistically significant, $F(1, 62)=308.95$, MSE=0.17, $p<0.001$, which indicates that, in accordance with published literature, the magnitude of the tilt aftereffect was larger at an adaptation angle of 15° than at 40°. In terms of ecstasy effects, there was no significant main effect of cohort, $F<1$, MSE=0.60, ns. and no significant interaction between the cohort and adaptation angle, $F(1, 62)=2.28$, MSE=0.17, $p=0.14$.

A more detailed investigation of the data, however, revealed a significant effect of ecstasy after adaptation to 40°, which was disguised by an effect of the number of days since the last use of amphetamines. Bivariate correlations between the main variables of interest and the number of days since the last use of ecstasy, alcohol, cannabis and amphetamines were conducted to determine if any of the observed differences between the cohorts were due to acute or residual effects of those drugs (Table 3). The only significant effect detected was that the magnitude of the tilt aftereffect at 40° was found to be correlated with the number of days since ecstasy users had last used amphetamines, $r(28)=0.435$, $p=0.02$, such that the more recently they had used the drug the smaller the aftereffect at 40°. This suggests that a significant difference between the cohorts may be revealed if ecstasy users who had recently used amphetamines had been excluded from the analysis. This was tested by dividing the ecstasy users cohort into two groups, namely, ecstasy users who had used amphetamines in the 61 days before testing (n=18, recent amphetamine users) and ecstasy users who had not used amphetamines for at least 115 days (n=12, abstinent amphetamine users). These criteria were used because the smallest of the resulting groups was large enough to conduct meaningful statistical tests (n=12) and because there was a convenient gap in the distribution of the last used amphetamines between 62 and 116 days before testing. To compare these two groups of ecstasy users to non-drug using controls (n=34), the average magnitude of the tilt aftereffect was calculated for each group (see Fig. 3). Mann–Whitney tests were used to compare the groups of ecstasy users to the controls because the sub-groups of ecstasy users had small sample sizes ($n<30$) with poorly distributed scores (Pagano 1998). The Mann–Whitney tests revealed that ecstasy users who had been abstinent from amphetamines for 115 days or more had a significantly larger tilt aftereffect than both non-drug using controls, U=120, $z=2.10$, $p=0.04$, and ecstasy users who had recently used amphetamines, $U=60$, $z=2.03$, $p=0.04$. Overall, these results indicate that the use of ecstasy in the absence of recent amphetamine use was associated with an increase in the magnitude of the tilt aftereffect. Thus, an ecstasy effect in the overall sample was disguised by the recent use of amphetamines.

Bivariate correlations were used to identify variables other than ecstasy that could account for the statistically significant differences identified in the previous paragraph. For the analysis of ecstasy users who had not used amphetamines for 115 days or more and non-drug using controls, the magnitude of the tilt aftereffect at 40° was not significantly correlated with estimated IQ, or any demographic, mental health, personality or alcohol use variable, all $p\geq0.12$.

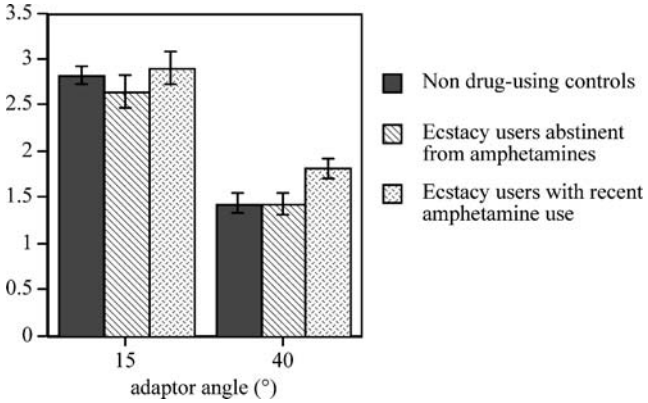

Fig. 3 Size of the tilt aftereffect for controls and ecstasy users split into sub-groups of those abstinent from amphetamines for at least 115 days and those using amphetamines recently (within 61 days). *Error bars* show ±1 SEM

For the analysis of ecstasy users who had recently used amphetamines compared to those who were abstinent from amphetamines, the only potential covariate revealed by the bivariate correlations was a non-significant trend towards a correlation between the magnitude of the tilt aftereffect at 40° and estimated IQ, $r(30)=-0.330$, $p=0.08$. The influence of estimated IQ on the difference between the two groups of ecstasy users was evaluated using regression analysis. This revealed that estimated IQ was a significant covariate, $\beta=-0.35$, $t(30)=2.09$, $p=0.05$. Once the influence of estimated IQ was taken into account, the difference between the two groups of ecstasy users on the magnitude of the tilt aftereffect at 40° remained statistically significant, $\beta=0.39$, $t(30)=2.36$, $p=0.03$. Further bivariate correlations within the ecstasy users groups revealed that the magnitude of the tilt aftereffect at 40° was not correlated with any cannabis use measure, all $p>0.30$.

The analysis of the recent use of amphetamines on the magnitude of the tilt aftereffect was then applied post-hoc to the 15° adaptation angle data to see if that measure was also influenced by the recent amphetamine use (see Fig. 3). The Mann–Whitney tests indicated that the magnitude of the tilt aftereffect at 15° for ecstasy users who had been abstinent from amphetamines for 115 days or more was not significantly different from either non-drug using controls, $U=195$, $z=0.238$, $p=0.81$, or ecstasy users who had recently used amphetamines, $U=87$, $z=0.889$, $p=0.37$.

The slopes at the PSE of the psychometric curves were analysed to see if the serotonergic-related decrease in the slopes of psychometric curves associated with temporal decisions in rats also occurs for visual behavioural responses in humans. The slopes in the present study were averaged across participants for the pre-adaptation and post-adaptation test at each adaptation angle (15° pre-adaptation, 15° post-adaptation, 40° pre-adaptation, 40° post-adaptation) and are displayed in Table 2. The slopes were shallower after adaptation than before, indicating reduced discriminability between similar orientations after adaptation. More interestingly, there was also a suggestion that ecstasy users tended to have slightly lower slopes (i.e. poorer discrimination) compared to non-drug using controls for both the pre- and post-adaptation tests. A mixed-model ANOVA analysis of test phase (pre-adaptation, post-adaptation), adaptation angle (15 and 40°) and cohort (ecstasy users, controls) revealed a significant main effect for the test phase, $F(1,62)=60.78$, MSE=1,548.73, $p<0.001$. However, the main effect of adaptation angle, $F(1,62)<1$, MSE=155.68, $p=0.73$, and cohort, $F(1,62)=1.64$, MSE=3,626.53 $p=0.21$, were not significant. Thus, there was no statistically significant support for ecstasy users having lower slopes than non-drug using controls despite there being slight trends in that direction.

A slightly odd result in Table 2 is that for ecstasy users, it appears that the pre-adaptation slopes measured before adaptation to 40° were less than the pre-adaptation slopes measured before the 15° adaptation: such a result would be strange because all pre-adaptation tests were identical and conducted in counterbalanced order. In fact, the difference was not statistically significant, $t(29)=1.79$, $p=0.08$. Furthermore, any such effect could arise only if ecstasy users had different temporal effects for the decay of the tilt aftereffect after adaptation to 40° compared to 15°, and there was no evidence that this occurred. An ANOVA for ecstasy users on pre-adaptation slopes revealed no main effect of temporal order (15° conducted first, 40° conducted first) and no interaction between temporal order and adaptation angle (15 and 40°), $F<1$.

In light of the effect of the recent use of amphetamines on the magnitude of the tilt aftereffect examined in the previous section, analysis of the effect of the recent use of amphetamines on the slopes was also conducted. Mann–Whitney tests revealed that after adaptation to 40°, the slopes for ecstasy users who had not recently used amphetamines (mean=43.08, SE=6.86) were not significantly different from the remaining ecstasy users (mean=57.80, SE=13.21) $U=99$, $z=0.381$, $p=0.70$, or non-drug using controls (mean=

Table 2 The mean (standard error of the mean) of the slope of the psychometric curves at the PSE for the pre-adaptation and post-adaptation tests, as a function of adaptation angle (15 and 40°) and cohort (controls, ecstasy users)

	Controls (n=34)	Ecstasy users (n=30)	p Values
15°			
Pre-adaptation	94.2 (9.9)	90.43 (10.3)	0.80
Post-adaptation	53.8 (6.0)	42.78 (5.3)	0.18
40°			
Pre-adaptation	96.7 (10.1)	73.65 (6.7)	0.07
Post-adaptation	52.7 (4.2)	51.91 (8.4)	0.93

Table 3 Dose dependence and recency of ecstasy and amphetamines: bivariate correlations between the magnitude of the tilt aftereffect as a function of adaptation angle (15 and 40°) and drug use (number of days since the last, lifetime dose, maximum monthly dose and the maximum ever dose of ecstasy in a single session) of ecstasy, amphetamines and cannabis within the ecstasy users group

	15°		40°	
	r(30)	*p* Values	*r*(30)	*p* Values
Ecstasy				
Last use	0.10	0.58	0.05	0.80
Lifetime dose	0.01	0.97	0.05	0.80
Maximum monthly dose	0.14	0.46	0.08	0.66
Maximum ever dose	−0.06	0.77	0.13	0.51
Amphetamines				
Last use	0.33	0.08	0.43	0.02
Lifetime dose	−0.02	0.93	−0.14	0.46
Maximum monthly dose	−0.05	0.78	−0.02	0.92
Maximum ever dose	−0.20	0.31	−0.15	0.44
Cannabis				
Last use	0.15	0.43	0.03	0.89
Lifetime dose	0.21	0.27	0.19	0.31
Maximum monthly dose	0.12	0.52	0.05	0.80
Maximum ever dose	−0.01	0.95	−0.05	0.78

52.69, SE=4.18) U=149, z=1.376, p=0.17. After adaptation to 15°, there was also no significant difference between the slopes for ecstasy users who had not recently used amphetamines (mean=37.49, SE=5.16) and the remainder of the ecstasy users (mean=46.30, SE=8.10) U=88, z=0.847, p=0.40, although there was a non-significant trend towards them having lower slopes than non-drug using controls, (mean=53.83, SE=6.03) U=131, z=1.826, p=0.07.

For the preadaptation tests, Mann–Whitney tests revealed that before adaptation to 40°, the slopes for ecstasy users who had not recently used amphetamines (mean=55.92, SE=4.05) were significantly less than both non-drug using controls (mean=96.68, SE=10.09) U=97, z=2.677, p=0.007, as well as the remaining ecstasy users (mean=85.47, SE=9.95) U=54, z=2.286, p=0.02. This is a potentially interesting result because the average lower slope in the psychometric curves may reflect reduced discriminability between similar orientations in ecstasy users, thus reflecting less lateral inhibition and broader tuning bandwidths of V1 neurons. This is consistent with the finding of a significant increase in the magnitude of the tilt-aftereffect for the same group of ecstasy users. However, before adaptation to 15°, there was a no significant difference between the slopes of ecstasy users who had not recently used amphetamines (mean=73.50, SE=9.80) and either non-drug using controls, (mean=94.15, SE=9.88) U=171.5, z=0.813, p=0.42, or other ecstasy users, (mean=101.71, SE=15.58) U=89, z=0.804, p=0.42. As with the similar finding with regard to the post-adaptation slopes for all ecstasy users, it is not clear why this discrepancy between the 15 and 40° pre-adaptation tests occurred, as the 15 and 40° pre-adaptation tests were identical and were conducted in counterbalanced order. In contrast to the earlier finding, there was an insufficient number of participants in the sub-groups of ecstasy users to reliably test for order effects. In addition, bivariate correlations between the magnitude of the tilt aftereffect in the 40° test for ecstasy users who had not recently used amphetamines and the preadaptation slopes before the 15 and 40° were not significant, $r(12)=-0.193$, p=0.55 and $r(12)=0.184$, p=0.57, respectively. This is unsurprising given the small number of ecstasy users in that sub-group (n=12). Further research is therefore required with large samples sizes to clarify these results before any conclusion regarding slopes can be made.

Discussion

The present study provides the first behavioural evidence of changes in low-level visual processing in ecstasy users associated with occipital lobe functioning. The results are consistent with the proposal that ecstasy-related damage to the serotonin system causes a decrease in the lateral inhibition between orientation sensitive neurons in visual area V1, which increases the tuning bandwidth of these neurons, which in turn results in an increase in the magnitude of the tilt aftereffect, especially after adaptation at 40° (Fig. 1).

The only other study that has examined the impact on the tilt aftereffect of changes to the serotonin system was Masini et al. (1990). That study found that the acute disruption to the serotonin system caused by tryptophan depletion resulted in a significant increase in the magnitude of the tilt aftereffect after adaptation to 15° (they did not test a 40° adaptation condition). The present study found that the impact on the serotonin system, which is thought to be associated with recreational ecstasy use, did not result in a significant increase in the tilt aftereffect at 15°. The difference between these findings may reflect that tryptophan depletion and ecstasy use are understood to disrupt the serotonin system in quite different ways. Ecstasy use is thought to result in the chronic depletion of serotonin in the brain and to render a dose-dependent proportion of serotonergic axons dysfunctional or even fully or partially destroyed (for review see Green et al. 2003). The chronic nature of this disruption leaves open the possibility of equally long-term compensatory changes occurring in the brain, such as the up-regulation of post-synaptic receptors, which may reduce the impact of the serotonergic damage (Buchert et al. 2003; Reneman et al. 2000a, b, 2002; Terriere et al. 1995). In contrast, tryptophan depletion is

thought to cause a severe but acute change in serotonin synthesis in the absence of lasting damage to the serotonergic axons. Therefore, while tryptophan-depletion studies provide a useful tool for indicating behavioural functions that may potentially be affected by ecstasy-related serotonergic changes, it remains quite possible that such functions remain relatively intact in ecstasy users.

The authors of the Masini et al. (1990) study interpreted their results as being consistent with the involvement of serotonin in lateral inhibition between neurons, such that a decrease in serotonergic functioning resulted in decreased lateral inhibition (and a corresponding increases is tuning bandwidth), thus increasing the magnitude of the tilt aftereffect. However, another plausible interpretation of both the Masini et al. (1990) results and the current findings is that serotonin is involved in the extent to which the sensitivity of neurons is reduced during adaptation. That is, a decrease in serotonergic functioning further decreases the post-adaptation sensitivity of the neurons, thus increasing the magnitude of the tilt aftereffect. We are currently investigating these different possible interpretations to determine the mechanism by which ecstasy and serotonin impact the tilt aftereffect. However, the findings in the present study clearly indicate significant changes on a behavioural measure of visual perception that is thought to reflect serotonergic functions in the occipital lobe.

An interesting finding in the present study was that the effect of ecstasy use was only apparent in people who had not recently used amphetamines (i.e. within the last 61 days) compared to non-drug using controls. These results suggest that the recent use of amphetamines moderate the effect of ecstasy use on the magnitude of the tilt aftereffect. There have been no reports published in literature of the impact of amphetamines directly on the tilt aftereffect. However, there is some indirect evidence that such an effect may exist. Amphetamines are known to cause long-term disruptive effects on the functioning of dopaminergic axons and axon terminals (McCann and Ricaurte 2004). The acute disruption of the dopamine system by administration of the dopaminergic antagonist haloperidol to healthy volunteers has been shown to reduce the magnitude of the tilt aftereffect (Harris et al. 1986). These findings are consistent with the apparent reduction in the magnitude of the tilt aftereffect associated with amphetamine use in the present study.

Other evidence that suggests that amphetamines and ecstasy may have opposing effects on low-level visual perception processes comes from an fMRI study of ecstasy users by Daumann et al. (2003). They found a reduction in the fMRI BOLD signal in the visual cortex of 'pure' ecstasy users, who denied regular use of other drugs, but not in ecstasy users who reported regular use of amphetamines and cannabis. The authors suggested that this may have occurred because amphetamines and/or cannabis had a contrary effect to that of ecstasy. This suggestion is supported by the findings in the present study, where the significant changes were only detected for ecstasy users who had not recently used amphetamines. Furthermore, the lack of any effect of cannabis in the present study suggests that it may be the recent use of amphetamines that is critical to disguising ecstasy-related effects and not cannabis.

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