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Original Investigation

Impaired perception of self-motion (heading) in abstinent ecstasy and marijuana users

M. Rizzo[1], C. T. J. Lamers[2], C. G. Sauer[3], J. G. Ramaekers[2], A. Bechara[1] and G. J. Andersen[3]

(1) Division of Neuroergonomics and Division of Behavioral Neurology and Cognitive Neuroscience, Department of Neurology, The University of Iowa Carver College of Medicine, Iowa City, IA, USA

(2) Experimental Psychopharmacology Unit, Department of Neurocognition, Brain and Behaviour Institute, Maastricht University, P.O. Box 616, 6200 Maastricht, The Netherlands

(3) Department of Psychology, University of California, Riverside, CA, USA

M. Rizzo
Email: matthew-rizzo@uiowa.edu

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Abstract

Rationale Illicit drug use can increase driver crash risk due to loss of control over vehicle trajectory. This study asks, does recreational use of ±3,4-Methylenedioxymethamphetamine (MDMA; ecstasy) and tetrahydrocannabinol (THC; marijuana) impair cognitive processes that help direct our safe movement through the world?

Objective This study assesses the residual effects of combined MDMA/THC use, and of THC use alone, upon perceived trajectory of travel.

Methods Perception of self-motion, or heading, from optical flow patterns was assessed using stimuli comprising random dot ground planes presented at three different densities and eight heading angles (1, 2, 4 and 8° to the left or right). On each trial, subjects reported if direction of travel was to the left or the right.

Results Results showed impairments in both drug groups, with the MDMA/THC group performing the worst.

Conclusions The finding that these psychoactive agents adversely affect heading perception, even in recently abstinent users, raises potential concerns about MDMA use and driving ability.

Keywords MDMA - Driving - THC - Substance abuse - Visual motion

Introduction

The widespread use of illicit drugs by young people raises many concerns, including the increased risk of cognitive impairments that can lead to vehicle crashes. Tetrahydrocannabinol (THC; in marijuana) is

probably the most prevalent drug besides alcohol identified in the bodies of impaired drivers and fatally injured drivers, yet benzodiazepines, cocaine, opiates, and amphetamines including ±3,4 Methylenedioxymethamphetamine (MDMA; in the party drug "Ecstasy")—are also detected regularly (Marquet et al. *1998*; Morland *2000*; Risser et al. *1998*; Verstraete and Puddu *2000*; Walsh et al. *1997*).

Although residual cognitive effects of MDMA have been studied extensively in drug users, these studies have focused primarily on mechanisms of memory, divided attention, semantic recognition, verbal reasoning, and learning. Little is known about whether MDMA specifically impairs visual motion perception, an ability that helps us navigate safely through the world without colliding with objects and obstacles during locomotion, as while walking and driving an automobile (Gibson *1950*; Rizzo and Dawling *1997*). The aim of this study is to examine a potential link between recreational combined MDMA/THC use, or THC use alone, and decline in motion perception abilities that play a role in driving behavior.

Psychoactive drugs may impair visual perception in alert individuals through effects on specific neurotransmitter systems. Nefazodone, an antidepressant that inhibits serotonin reuptake and blocks 5-HT2 receptors, may cause a transient defect of visual motion perception (Horton and Trobe *1999*). Motion-perception defects are associated with increased crash risk in simulated collision avoidance scenarios in drivers with mild Alzheimer's disease (Rizzo et al. *2001*) and may underlie the increased risk of vehicle crashes in drivers who use alcohol (Nawrot *2003*), prescription drugs, or recreational drugs of abuse (Rizzo *2004*). MDMA affects serotonergic mechanisms (Lyles and Cadet *2003*; Mechan et al. *2002*; Ricaurte et al. *1993*; White et al. *1996*) with potential neurotoxic effects like those of nefazodone.

This study assesses effects of MDMA on heading, the perceived trajectory of locomotion, from patterns of optical flow. Gibson (*1950*) argued that the perspective transformation of the optic array, or optical flow, provides information for determining heading, the direction of observer motion. Heading information helps guide us when we move in the world and is of key importance for perceptual tasks such as steering a vehicle (e.g., Andersen and Saidpour *1999*; Rushton et al. *1999*; Loomis and Beall *1998*). Because effects attributed to MDMA (Gouzoulis-Mayfrank et al. *2000*; Verkes et al. *2001*) might be due to other drugs, particularly THC in marijuana (Croft et al. *2001*), this study of heading perception in MDMA users controls for concurrent use of THC and other drugs.

Previous research on the perception of heading from optical flow has examined a number of different sources of information and has primarily focused on the role of expansion information from optical flow. Early theoretical analyses focused on the use of local velocity information for estimating the heading direction (Longuet-Higgins and Prazdny *1980*). More recent analyses, however, have focused on models in which local velocities are spatially combined or pooled to estimate the heading direction (Dyre and Andersen *1997*; Perrone and Stone *1998*). These models were motivated by neurophysiological studies (Duffy and Wurtz *1991*; Saito et al. *1986*) that showed that area MST (medial superior temporal area of primate visual cortex) has cells that respond to large field expansion patterns by pooling the output of cells that respond to local velocities in area MT (middle temporal area of primate extrastriate visual cortex). More recently, Andersen and Saidpour (*2002*) demonstrated that the perception of heading by human observers required pooling local velocities over regions of at least an 8.5° visual angle. The necessity of spatially pooling velocities for the perception of heading can be contrasted to other high-level motion tasks that are based on local velocities. For example, the perception of structure from motion (Braunstein and Anderson *1984*) is based on using local velocities to recover deformation components of optical flow (Koenderink *1986*). In addition to examining changes in the perception of heading associated with THC and MDMA use, we also compare performance of heading judgments, which require spatially pooling velocity information, with performance in a structure from motion task that does not require spatially pooling velocity information.

Methods

Forty-two volunteers (age range 21–42 years old) were recruited and inducted into one of three test groups: combined MDMA and marijuana users (MDMA/THC), marijuana users (THC), and non-drug using controls (Table 1). Controls (six female, nine male) had not used illicit drugs except marijuana on five or fewer occasions but not within the last 365 days. THC users (five female, ten male) had never used MDMA and had used THC at least ten times; the occasions they used other drugs did not exceed their THC use. MDMA/THC polydrug users (seven male, five female) had a history of THC use and had used MDMA on at least ten occasions. Participants were asked to abstain from drug use on the day of testing. Exclusion criteria included (1) alcohol or drug dependence; (2) excessive use of drugs other than THC and MDMA (frequency of other drugs should not exceed that of the inclusion criterion drugs); (3) serious physical or psychological illness; and (4) current use of prescribed psychoactive drugs. Subject characteristics are presented in Table 1.

Table 1 Mean (SD) characteristics of THC users, MDMA/THC users, and non-drug user controls and their statistics

Variable	Mean (SD)			ANOVA *F*(2,39)	Tukey's HSD post-hoc test significance (*P*)		
	Controls, *n*=15	THC users, *n*=15	MDMA/THC users, *n*=12	Group effect	Control THC	Control MDMA/THC	THC MDMA/THC
Age (years)	24.0 (3.2)	24.3 (5.3)	22.8 (2.3)	0.569			
Education (years)	16.5 (1.2)	15.3 (1.4)	15.5 (0.7)	4.092*	0.028	ns	ns
Verbal IQ (NART)	109.1 (4.5)	108.8 (4.7)	104.3 (6.8)	3.055			
Alcohol (days)	318 (332)	780 (472)	824 (542)	5.561**	0.020	0.016	ns
THC (days)	1.2 (2.1)	1,582 (1,433)	855 (874)	9.854**	0.000	ns	ns
Days of THC abstinence	1,232.3 (1,377.6)	15.7 (46.4)	44.6 (106.5)	12.115**	0.000	0.000	ns
MDMA/Ecstasy	0.0 (0.0)	0.0 (0.0)	36.9 (32.1)	20.096**	ns	0.000	0.000
Days of MDMA abstinence			226.9 (134.0)				
Cocaine	0.0 (0.0)	4.5 (10.5)	14.3 (21.8)	4.046*	ns	0.021	ns
psilocybin	0.0 (0.0)	11.4 (17.2)	8.9 (6.6)	2.847			
LSD	0.0 (0.0)	14.4 (20.1)	6.3 (7.8)	1.306			
Opium	0.0 (0.0)	3.3 (12.9)	0.0 (0.0)	0.895			
Methamphetamines	0.0 (0.0)	0.0 (0.0)	0.1 (0.3)	1.266			
Sedatives	0.0 (0.0)	0.5 (0.1)	0.0 (0.0)	0.895			
Nitrous gas	0.0 (0.0)	0.3 (1.0)	0.0 (0.0)	0.895			

Alcohol and drug use are described as lifetime use. Group comparisons are only reported if the overall effect of the group

was $\leq$0.05. They are reported as not significant (ns) if P>0.05

*$P \leq 0.05$

**$P \leq 0.01$

To operationalize exclusion criteria, a checklist was used to gather specific information about any reported medical or psychological problems in the 5 years before the study. Psychiatric history was assessed using the Structured Clinical Interview for DSM-IV (the SCID) and a questionnaire (Goldberg *1972*). Medication type, dose, and frequency of use were assessed using standardized procedures (Cardiovascular Health Study 1989). Assessment of illicit drug use was based on self-report. Also, a urine drug screen assessed THC, MDMA/Ecstasy, cocaine, psilocybin, LSD, opium, methamphetamines, sedatives, and nitrous gas (UA-SCREEN Instant Drug Tests, http://www.ua-screen.com/index.html).

The study was approved by the Institutional Review Board of the University of Iowa Hospital Clinics and conducted in accord with the declaration of Helsinki (1969) and its subsequent amendments.

Because drug use might predispose an individual to sleep disturbance and acute fatigue, we administered the Stanford Sleepiness Scale (SSS) to all participants. The SSS asks subjects to rate their current state of wakefulness/sleepiness on a 7-point scale (1 is most alert, 7 is almost asleep). Scores on the SSS have been shown to correlate with alertness on neuropsychological tests (Hoddes et al. *1973*). Visual function assessment included static visual acuity and static spatial contrast sensitivity. Static visual acuity for identifying single letters was measured under standard photopic conditions using a Sloane chart (Owsley *1994*). Static spatial contrast sensitivity was assessed under standard photopic conditions using the Pelli–Robson chart. This test measures the amount of contrast needed to identify letters subtending $\sim$2.8° of visual angle at a distance of 1 m (Mantyjarvi and Laitinen *2001*), i.e., in the low to medium spatial frequency range near the peak of the contrast sensitivity function.

The perception of structure from motion involved stimulus figures that comprised orthographic projections of spatially random dots on a mathematical model of a clockwise or counterclockwise rotating sphere or cube (a diamond shape rotating on its vertex). Subjects were asked to report the shape of the rotating figure presented in each trial. To prevent shape identification from non-motion cues and to index the difficulty of the task, varying amounts of random dot noise were added to a background region surrounding the figure (Rizzo et al. *1995*). The threshold of density of dots needed to correctly identify objects was the dependent variable. This test is sensitive to defects in motion perception following cerebral lesions (Rizzo et al. *1995*). Attention and processing speed were measured with the Visual Attention Analyzer (Model 3000) in a task known as the Useful Field of View (UFOV) test (Ball et al. *1993*). The UFOV test depends on four sub-tests. Sub-test 1 measures processing speed to identify a single visual target presented in the center of the computer screen. Sub-test 2 assesses divided attention and requires identification of a central target and localization of a simultaneously presented peripheral target. Sub-test 3 assesses selective attention abilities and is identical to Sub-test 2, except that the peripheral target is embedded amid distracters. Sub-test 4 also assessed selective attention, but is more difficult than Sub-test 3 because the central task requires making a same–different discrimination between two targets (selective attention-2). Dependent variables were thresholds for processing speed, divided attention, selective attention, and selective attention-2. Threshold scores of the four sub-tasks ranged from 16 ms (no impairment) to 90 ms (maximum impairment).

In the Heading Task (Fig. 1), the displays simulated observer motion over a ground plane of randomly placed white dots presented against a black background. The dimensions of the space were 1,000 by 1,000 by 1,191 units, with the simulated eye position of the observer at 100 units. The stimuli were presented on a 25.8° by 34.7° computer display. The simulated speed was 25 m/s. Observer motion was

–8, –4, –2, –1, 1, 2, 4, or 8° relative to a vertical bar presented at the end of the trial. The vertical bar appeared 5° to the left or right of the midline of the display. Display update was 50 frames/s, with the display duration at 3 s. Three dot densities were examined: 0.035, 0.243, and 0.451 dots/deg^2. We will refer to these conditions as the low-, medium-, and high-density conditions, respectively. Subjects were asked to report perceived direction of their travel to the left or the right of a vertical post by pressing response keys. Subjects were presented ten replications of each combination of heading angle and dot density in random order. Right and left heading angles were combined into one score, as pilot testing showed no lateralized performance difference. The dependent measure was percent correct.

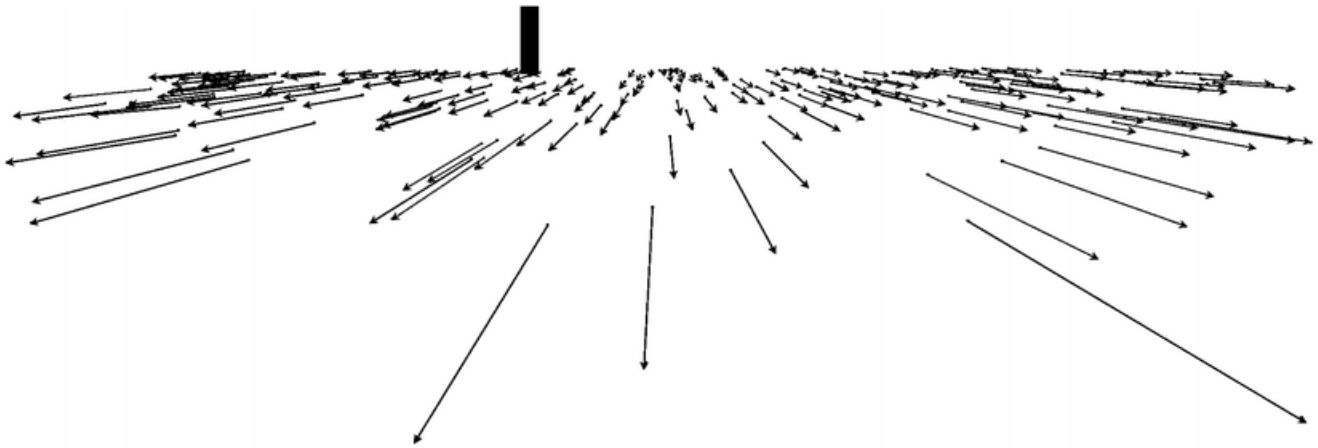


Fig. 1 Schematic illustration of the heading task. Each vector represents the change in position of a texture element in the display during forward motion. The subject's task was to judge the direction of observer motion relative to the *vertical bar*. In the illustration, the correct response is the direction to the right of the bar

Data analyses

We compared the demographic factors and performance factors in the three groups of participants using standard statistical procedures. Demographic factors included age, education, alcohol and drug use, visual functions, and sleepiness. We compared thresholds for the main outcome measures on the perception of structure from motion task and the perception of heading task in the different groups. We adjusted these outcomes for potential confounding factors, such as concomitant alcohol use, as outlined in the results.

Results

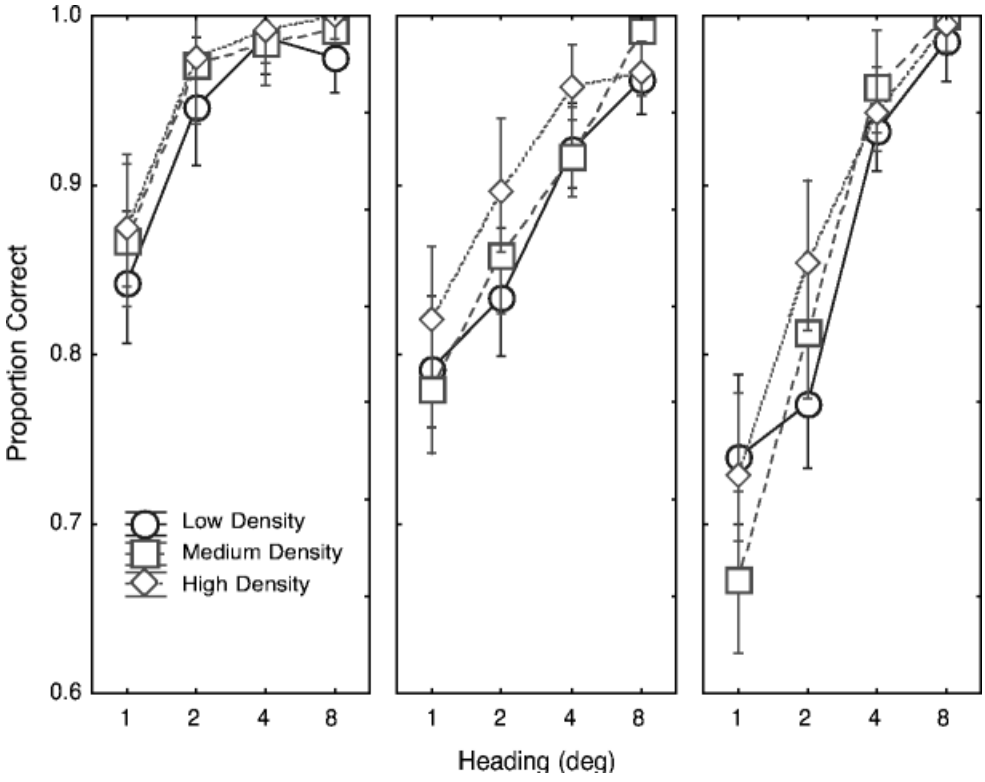
The results (Table 1) revealed that groups did not differ significantly in age. Tukey's HSD ("Honestly Significantly Different") procedure revealed that THC users had 1.2 fewer years of education than controls, but National Adult Reading Test (NART) scores, which are considered to be good estimates of verbal IQ (Grober and Sliwinski *1991*), did not differ significantly between groups. Because education is closely related to IQ, especially verbal IQ, this suggests that the slight educational difference was not meaningful from cognitive and clinical perspectives. THC users and MDMA/THC users had consumed alcohol on more occasions than controls. Alcohol use did not differ significantly between THC and MDMA/THC users. Of note, there was a trend toward higher frequency of THC use in THC users than in MDMA/THC users (P=0.074). All controls produced negative drug screens, but seven MDMA/THC

users (58%) and 12 THC users (80%) produced positive drug screens for THC. Average days of THC abstinence was 15.7 (range 1–183 days) in THC users and 44.6 (range 1–365 days) in MDMA/THC users. Tukey's HSD procedure showed that the duration of abstinence from THC in days did not differ between THC and MDMA/THC users.

Subjects showed normal visual functions. Median static visual acuity was 20/15 in each group and did not differ between specific groups. Mean contrast sensitivity was 1.90 for all groups and did not differ between groups. The groups did not differ in performance on tests of attention or sleep.

Mean threshold for structure from motion was 8.9 (SD 2.9) for controls, 8.9 (SD 2.7) for THC users, and 8.6 (SD 2.9) in MDMA/THC users and did not differ between groups.

Most importantly, the heading results revealed impairments in the drug groups. Mean heading accuracy was calculated for each subject in each condition and analyzed using a three (normal, THC, and MDMA/THC groups) by three (low-, medium-, and high-density levels) by four (1, 2, 4, or 8° heading angle) Analysis of Variance (ANOVA). Figure 2 shows that performance in all groups improved with an increase in heading angle, $F(3,117)=64.9$, $P<0.01$. The main effect of display density was also significant, $F(2,78)=5.4$, $P<0.01$, indicating a slight improvement in heading accuracy with an increase in density. The interaction between group and heading angle was significant, $F(6,117)=4.5$, $P<0.01$, and is shown in Fig. 3. Plots of proportion correct and heading angle showed worse performance in both drug groups compared to controls at all but the 8° heading angle ($P<0.05$). The MDMA/THC group had significantly poorer performance than the control or THC groups at the 1 and 2° heading angle conditions, $P<0.05$. Of note, the MDMA/THC users performed worse than the THC users, even though the THC group tended to use THC more frequently and recently than the MDMA/THC group. We used Analysis of Covariance (ANCOVA) to assess the effects of alcohol and cocaine use on heading judgments in MDMA/THC. The main effect of heading [$F(3,117)=20.3$] and density [$F(2,78)=14.4$] were statistically significant, $P<0.01$. The two-way interaction between group and heading angle was also statistically significant, $F(6,117)=4.51$, $P<0.01$. When controlling for alcohol and cocaine use, the results showed persistent effects of density and heading angle, as well as decreased performance for the MDMA/THC group, at small heading angles.



Normal THC MDMA

Fig. 2 Performance of the control, MDMA/THC, and THC groups is shown as a function of heading angle. The effect of display density is also shown

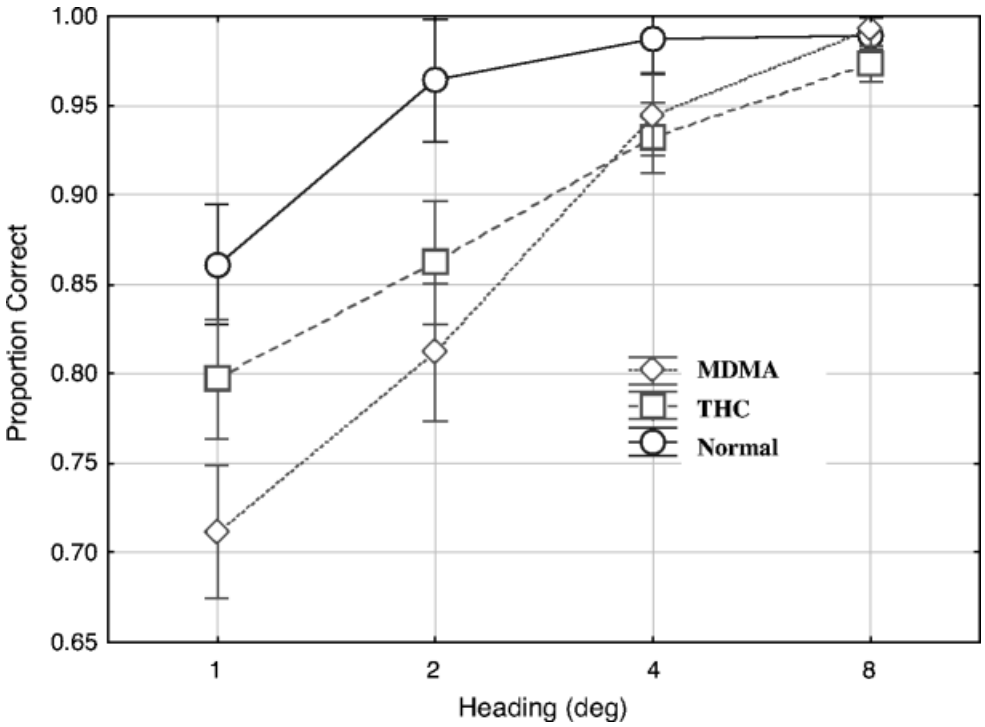


Fig. 3 The figure illustrates the interaction between group and heading angle. Both drug groups had significantly worse performance than the control group at the 1, 2, and 4° heading angles. The MDMA/THC group had significantly poorer performance than the control or THC groups at the 1° and 2° heading angle conditions

Discussion

The findings in this study indicate that psychoactive agents adversely affect heading perception in recreational drug users, despite recent drug abstinence, and these effects appear to be additive in MDMA and THC users. Despite the poorer performance in the heading task for the MDMA/THC users, as compared to the other two groups, no significant difference was obtained for the three groups on the structure from motion task. Results from empirical and theoretical research on the perception of heading suggest that this task requires combining or pooling velocity information over space to perform the task. In contrast, structure from motion is performed by comparisons of local neighborhood velocities. This suggests that MDMA/THC users may have difficulty spatially integrating velocity information.

In this study, basic visual functions fell within normal limits in all groups. Repeated users of THC and MDMA/THC did not show impairment of visual acuity, spatial contrast sensitivity, visual processing speed, and attention compared to non-drug using controls. This resembles the findings of no differences in attentional function between MDMA users, non-drug users, and polydrug users (Rodgers *2000*). In MDMA/THC users, however, heading was impaired but structure from motion preserved. Structure from motion and heading perception both involve low-level processing of motion cues, but would appear to involve dissociable, higher-level processes. Structure from motion is based on analyzing local

velocities, whereas heading is based on spatially integrating velocities. In addition, these tasks serve different functions. Structure from motion is used for shape/object recognition, whereas heading is used to move through the environment.

Because several drug users in this study showed positive THC drug screens, effects in drug users might have resulted from residual effects of recent THC use rather than long-lasting neural changes. Yet the number of days of abstinence of THC did not differ between drug groups, suggesting that the current results do not reflect residual effects of recent THC use. Moreover, MDMA users performed worse than THC users on the heading task although they tended to use less THC than the THC group. There was no significant difference in alcohol use between the two drug-using groups, although both drug groups reported greater alcohol use than non-drug using controls, and the MDMA/THC group reported greater cocaine use. However, differences in heading perception between groups persisted after adjusting for use of alcohol and cocaine.

MDMA neurotoxicity in animals has been observed with doses ranging from 15 mg/kg once daily to 20 mg/kg twice daily for 4 consecutive days (Aguirre et al. *1997*; Colado et al. *1999*; Mechan et al. *2002*; Ricaurte et al. *1993*). Brain degeneration in human MDMA users may reflect serotonin depletion and lead to impairments in attention, memory, and executive functions even in abstinent MDMA users (Krystal et al. *1992*; Lyles and Cadet *2003*; McCann et al. *1999*; Parrott *2001*; Parrott et al. *1998*; Wareing et al. *2000*). Serotonin may help regulate impulsivity and aggression, and increased impulsivity was observed in abstinent MDMA users (McCann et al. *2000*; McCann et al. *1994*; Morgan *1998*; Spreux-Varoquaux et al. *2001*).

Primate visual cortex is densely innervated by serotonin-containing fibers (de Lima et al. *1988*) that would be affected by MDMA. MDMA use can impair 8-Hz photic flicker-induced visual cortical activation (Cowan et al. *2001*), measured by fMRI blood oxygen level-dependent (BOLD) methods. Visual processing deficits with MDMA may be compared with deficits reported with nefazodone, which inhibits serotonin reuptake and blocks 5-HT2 receptors. Therapeutic doses of nefazodone and the related drug trazodone each reduce the ability to perceive the transient information in flickering displays (Christman and Setterberg *2003*). A woman receiving nefazodone for depression for 6–8 weeks, 3 years earlier, complained of central and peripheral vision loss (Luu et al. *2003*). Electroretinographic profiles and evoked responses to two-frame motion suggested a retinal abnormality. Two patients receiving nefazodone for depression reported that moving objects were followed by multiple "freeze-frame" images and similar visual trails (Horton and Trobe *1999*). Their complaints ceased after nefazodone was reduced or stopped and were equated with akinetopsia, a cerebral disorder of motion perception that affects processing of multiple visual cue types (Rizzo et al. *1995*).

Impaired perception of the path of self-motion (heading) in drug users in this study may involve toxic involvement of serotonin and other receptors (e.g., acetylcholine with THC) at several levels from retina to cortex. A magnocellular (or M-pathway) arises from retinal ganglion cells that have large, fast-conducting axons that convey information about transient visual signals, such as flicker and motion, to primary visual cortex and visual association cortex, including middle temporal area MT (V5) and the medial superior temporal (MST) area (Allman and Kaas *1971*). Lesions of MT (V5) produce a relatively selective deficit for motion perception in the contralateral visual hemifield, which recovers within a few weeks, depending upon lesion extent and white matter involvement (Newsome and Paré *1988*). Human motion processing deficits have been attributed to lesions in a human homolog of the monkey's area MT complex (thought to be located around the junction between the temporal, parietal, and occipital lobes; Zeki *1991*; Zihl et al. *1991*), as in the akinetopsic patient L.M. (Zihl et al. *1983*), who showed impaired ability to use motion cues in several motion-related tasks (Rizzo et al. *1995*). Other areas also process motion (Orban et al. *1995*; Grill-Spector et al. *2001*), and motion apperception has been reported with lesions in parietal insula and midline cerebellum (Nawrot *2003*; Nawrot and Rizzo *1998*; Nawrot et al. *2000*), with bilateral vestibular lesions (Grunbauer et al. *1998*), and, as mentioned above, with the drug

nefazodone.

This study indicates that the drug of abuse Ecstasy affects motion processing, although the capacity and timeline for recovery remain a research issue (Morgan et al. *2002*; Passie et al. *2002*). The important point is that residual effects can impair visuoperceptual processes that mediate safety-critical tasks such as automobile driving.

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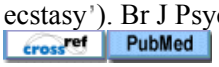

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