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Neural mechanisms underlying ecstasy-related attentional bias

Gloria M.P. Roberts [a,*], Hugh Garavan [a,b,c]

[a] School of Psychology and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland
[b] Department of Psychiatry, University of Vermont, Burlington, VT, USA
[c] Department of Psychology, University of Vermont, Burlington, VT, USA

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ABSTRACT

Conditioned responses to cues associated with drug taking play a pivotal role in a number of theories of drug addiction. This study examined whether attentional biases towards drug-related cues exist in recreational drug users who predominantly used ecstasy (3,4-methylenedioxymethamphetamine). Experiment 1 compared 30 ecstasy users, 25 cannabis users, and 30 controls in an attentional distraction task in which neutral, evocative, and ecstasy-related pictures were presented within a coloured border, requiring participants to respond as quickly as possible to the border colour. Experiment 2 employed functional magnetic resonance imaging (fMRI) and the attentional distraction task and tested 20 ecstasy users and 20 controls. Experiment 1 revealed significant response speed interference by the ecstasy-related pictures in the ecstasy users only. Experiment 2 revealed increased prefrontal and occipital activity in ecstasy users in all conditions. Activations in response to the ecstasy stimuli in these regions showed an apparent antagonism whereby ecstasy users, relative to controls, showed increased occipital but decreased right prefrontal activation. These results are interpreted to reflect increased visual processing of, and decreased prefrontal control over, the irrelevant but salient ecstasy-related stimuli. These results suggest that right inferior frontal cortex may play an important role in controlling drug-related attentional biases and may thus play an important role in mediating control over drug usage.

1. Introduction

Compromised ability to exert control over drug urges and drug-seeking behaviour is a distinguishing feature of addiction. The extent to which drug-related stimuli acquire the ability to initiate drug-seeking behaviour is a concept central to many theories of addiction. According to the incentive-salience theory (Robinson and Berridge, 1993), drug users acquire hypersensitivity to drug-related cues associated with drug use. The heightened salience of these cues can "grab" attention leading to drug-seeking, a cascade effect that may not even require conscious awareness of the drug cues (Childress et al., 2008).

There have been a number of behavioural studies which have demonstrated an attentional bias towards drug-related stimuli in cannabis (Field et al., 2004; Field, 2005), cocaine (Hester et al., 2006; Vadhan et al., 2007), heroin (Franken et al., 2000, 2004; Lubman et al., 2004), nicotine (Mogg et al., 2003, 2005; Munafo et al., 2003; Waters et al., 2003; Drobes et al., 2006; Bradley et al., 2008; Janes et al., 2010; Luijten et al., 2011) and alcohol users (Townshend and Duka, 2001; Lusher et al., 2004). The extent to which users of ecstasy (3,4-methylenedioxymethamphetamine) show similar biases for ecstasy-related stimuli has not been tested, but there is evidence of ecstasy-related reward-processing biases in other aspects of drug-related behaviour that involve the mesocorticolimbic system. For example, *in vivo* microdialysis studies in rats showed that an acute ecstasy administration caused marked increases in both dopamine (DA) and serotonin (5-HT) in the striatum and nucleus accumbens (Yamamoto and Spanos, 1988; White et al., 1994). Ecstasy is self-administered by rats (Daniela et al., 2004) and nonhuman primates (Fantegrossi et al., 2002, 2004; Feltenstein and See, 2007) and, in humans, an acute dose of ecstasy causes positive subjective effects such as a feeling of euphoria (Cami and Farre, 2002). Thus, as the mesocorticolimbic system is activated in response to ecstasy administration and has been activated in response to drug-related cues both in animals (Duvauchelle et al., 2000; Weiss et al., 2000; Ito et al., 2002; Phillips et al., 2003; Di Ciano and Everitt, 2004; Kiyatkin and Stein, 1996; Vanderschuren et al., 2005) and humans (Maas et al., 1998; Garavan et al., 2000; Tapert et al., 2003; Grusser et al., 2004; Volkow, 2006; Wong et al., 2006; Zijlstra et al., 2008), it follows that a similar salience effect for ecstasy-related cues may be observed in ecstasy users.

Functional magnetic resonance imaging (fMRI) has revealed that smoking abstinence increases brain sensitivity to smoking-related cues in regions involved in reward and motivation (McClernon et al., 2007). This may account for the finding that exposure to such cues is an important precipitant of smoking lapse and relapse (Shiffman et al., 1996). In accordance with this finding, there is evidence that cessation treatments designed to devalue smoking (McClernon et al., 2007) and alcohol-related cues (Schoenmakers and Wiers, 2010) decrease brain cue reactivity and that baseline cue reactivity may be predictive of

* Corresponding author. Tel.: +353 2938 28324; fax: +353 29382 8208.
E-mail address: robertsg@tcd.ie (G.M.P. Roberts).

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Table 1
Experiment 2: group demographics and drug use history.

	Ecstasy ($n=30$)	Cannabis ($n=25$)	Controls ($n=30$)
Age	22.1 ± 0.5	20.7 ± 0.5	22.3 ± 0.6
Years of education	16.5 ± 0.4	16.0 ± 0.3	16.5 ± 0.4
Verbal intelligence score (NART)	124.1 ± 0.7	124.4 ± 0.5	125.9 ± 0.5
Beck Depression Inventory II score	8.1 ± 1.1*	8 ± 5*	4.4 ± 0.8
Females/males	12/18	15/10	12/18
Ecstasy use in the last month (no. of times)	2.0 ± 0.3	na	na
Pills in last month (number)	7.6 ± 1.3	na	na
Last ecstasy use (days)	21.4 ± 4.4	na	na
Lifetime pills (number)	263.3 ± 63.5	na	na
Pills in last year (number)	61.7 ± 9.9	na	na
Years of cannabis use	5.5 ± 0.6 ($n=27$)	4.2 ± 0.4	na
Days of use in last month (number)	7.9 ± 1.6 ($n=27$)	8.8 ± 1.4	na
Joints in last month (number)	22.9 ± 6.6 ($n=27$)	18.9 ± 6.2	na
Last cannabis use (days)	40.8 ± 26.7 ($n=27$)	73.1 ± 55.9	na
Lifetime joints (number)	835.3 ± 224 ($n=27$)	1093.8 ± 220.4	na
Years of alcohol use	7.0 ± 0.5	5.2 ± 0.4	6.1 ± 0.7
Alcohol use in last month (no. of days)	8.6 ± 0.8	8.5 ± 1.1	6.8 ± 0.9
Average units of alcohol per week	2.2 ± 0.1	2.3 ± 1.4	1.9 ± 0.2
Years of nicotine use	3.4 ± 0.7 ($n=16$)	3.3 ± 0.3 ($n=18$)	1.9 ± 0.6 ($n=10$)

* $p < 0.05$.

cessation outcomes. As, to date, only a small number of neuroimaging studies have focused on drug-cue tasks, little is known about the neurobiological processing of these cues in users of "recreational" drugs such as ecstasy. Moreover, despite its potential clinical relevance, little is known about the neurobiology underlying how individuals combat the distracting effects of drug cues.

To investigate an attentional bias effect in ecstasy users, the current experiment used an attentional distraction paradigm in which individuals were required to make stimulus–response selections in the presence of irrelevant but potentially interfering neutral, evocative and drug-related stimuli. Experiment 1 investigated the processing of drug-related stimuli in demographically matched polysubstance users who predominantly used ecstasy, cannabis users, and controls. As the recreational ecstasy users were concomitant cannabis users, the cannabis group was included to identify ecstasy-specific effects. Experiment 2 probed neural activity using a modified version of the same attentional distraction task. The study had two motivations. First, would the same attentional biases that have been reported for "harder" drugs that are considered more harmful and more likely to lead to dependence (Nutt et al., 2007) also be observed for ecstasy users? If so, this would suggest that these biases are general to many drugs of abuse and may, indeed, be an integral part of the cognitive profile of drug users. Second, performance on tasks like these, while showing robust evidence of interference from drug stimuli, tends not to show catastrophically poor performance as, typically, drug users are able to exert sufficient levels of cognitive control in order to perform adequately (e.g., responses tend to be mostly accurate, albeit slower). Given the relationship between attentional biases towards drug cues and relapse, understanding the neurobiology of how cognitive control over these biases is accomplished may have both theoretical and therapeutic importance.

2. Experiment 1

2.1. Methods

2.1.1. Participants

The ecstasy group included 30 polysubstance users who predominantly used ecstasy; the cannabis group included 25 users of cannabis that matched the ecstasy group in cannabis use and had no other history of illicit drug use; and the drug-naïve group was comprised of 30 participants with no history of illicit drug use. Participants were recruited by poster recruitment. All participants underwent a phone screening, during which past illicit and prescribed drug use was quantified, and information concerning past and present psychiatric and neurological well-being was taken. Participants in the drug-naïve group were required to have never used any illicit substance. Participants in the ecstasy-using group were required to be current users of ecstasy and to have consumed at least 40 ecstasy tablets over a period of a year, but not necessarily over the immediately preceding year. With the exception of cannabis, participants in the ecstasy using group were excluded if they used any other illicit drugs on more than 10 occasions in their lifetime (or more than 15 times if the substance had not been used in the 5 years preceding the study) and were required to be abstinent of these drugs for a minimum period of 10 weeks prior to testing. Participants were also excluded if they had reported either past or present neurological or psychiatric problems. As daily smoking of cannabis is part of the lifestyle of most club drug users (Daumann et al., 2003), participants in the ecstasy-using group were not excluded for cannabis use and were not required to abstain from smoking cannabis prior to participation. Ecstasy users were requested to abstain from ecstasy for at least 48 h prior to study participation. Given this abstinence period, all participants provided a negative urine sample for ecstasy. All participants who reported cannabis use at any stage in the 30 days prior to study participation tested positive for cannabis ($n=22$ in the ecstasy group, and $n=23$ in the cannabis group). Additional screening for methadone, benzodiazepines, cocaine, opiates, barbiturates and tricyclic antidepressants (urinalysis drug test device purchased from Cozart Rapiscan, UK) revealed negative urine analysis results in all three groups. All participants gave informed consent and the study was approved by the School of Psychology in Trinity College Dublin.

Table 1 shows the group demographics and drug use history for the ecstasy group, cannabis group and controls. The groups did not differ in verbal IQ as assessed by the National Adult Reading Test (NART), age, gender, years of education, alcohol, nicotine, or other illicit drug use with the expected exception of ecstasy and cannabis as specified in the selection criteria. The cannabis use measures did not differ between the ecstasy group and the cannabis group. The ecstasy and cannabis groups reported higher Beck Depression Inventory (BDI) scores compared to controls but were similar to each other on this measure.[1]

2.1.2. Stimuli and behavioural protocol

The task was programmed using *E-Prime version 1.1* (Psychology Software Tools, Pittsburgh, PA, USA). Participants viewed pictures of three different types of stimulus category: neutral, evocative, and ecstasy-related. Neutral and evocative stimuli were photographs from the International Affective Picture System (IAPS) (Lang et al., 1999), and ecstasy-related stimuli were taken from multiple sources from the internet. Evocative pictures depicted a variety of aversive stimuli (e.g., accidents, vermin, domestic violence, and mutilated bodies; mean valence = 2.6 ± 1.2, mean arousal = 5.3 ± 1.4). Neutral stimuli consisted of a range of stimuli from different semantic categories (e.g., chair, iron, plant pot, neutral

[1] To address potential problems caused by the different distribution of males and females in the cannabis group, all analyses were repeated and revealed the same effects when each group was restricted to 12 females and 10 males.