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Title

Evidence of increased activation underlying cognitive control in ecstasy and cannabis users.

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Evidence suggests that users of ecstasy (3,4-methylenedioxymethamphetamine) have behavioural and cognitive deficits and show increased impulsivity. Impulse control impairments have been shown to be common to a number of addictive behaviours and may constitute a risk factor for drug abuse and dependence. The aim of this study was to investigate brain activation during response inhibition and performance monitoring in current recreational drug users who predominantly used ecstasy. Twenty drug users (ten female) and twenty healthy controls were scanned during performance of a response inhibition GO/NOGO task using functional magnetic resonance imaging. No performance deficits were evident. However, the drug user group revealed elevated frontal and parietal BOLD response during successful inhibitions, and temporal, frontal, and cingulate hyperactivity during commission errors. In addition, the users showed reduced deactivation in the default-mode network during task performance. Whether contributing to or arising from drug use, these results reveal dysregulation in brain regions subserving cognitive control and default mode processes in current recreational drug users mirroring effects previously observed for “harder” drugs of abuse.

Introduction

Heightened impulsivity is a feature of a number of clinical disorders including psychopathy, attention deficit hyperactivity disorder, bulimia nervosa, and drug abuse (American Psychiatric Association, 1994). In relation to the regular use of ecstasy (3,4-methylenedioxymethamphetamine) impulsivity has received particular attention as aggressive behaviours (Gerra et al 2000) and serotonergic depletion in animals and humans (Mc Cann et al 1994; Hatzidimitriou et al 1999; Reneman et al 2001; Gudelsky and Yamamoto, 2008) have been associated with both ecstasy use and impulsivity. However, the evidence for impulse control impairments in recreational drug users who predominantly used ecstasy is inconsistent. For example, ecstasy users revealed elevated impulsivity on the Matching Familiar Figures Test (MFFT) (Morgan et al 1998; Morgan et al 2002; Morgan et al 2006; Quednow et al 2007) and on trait impulsivity (Morgan et al 1998; Parrott, 2000b; Butler and Montgomery, 2004) in comparison to drug-naïve controls. However, there are reports of failures to replicate these deficits on a response inhibition GO/NOGO task (Fox et al 2002; Gouzoulis-Mayfrank et al 2003), a Stop Signal Test (von Geusau et al 2004), Stroop tests (Dafters, 2006; Vollenweider 1998), and on trait impulsivity (Clark et al, 2008). Previous studies also found that polydrug users, including users who had or had not used ecstasy, reported similar levels of impulsivity (Morgan et al 1998; Tuchtenhagen et al 2000; Daumann et al 2001; Morgan et al 2002; Butler and Dafters et al 2004; Hoshi et al 2007a; Hanson et al 2008), suggesting that elevated impulsivity may characterise drug users in general and not specifically those who have a history of ecstasy use.

Impulsivity is a complex and multidimensional psychological construct (Gerbing et al. 1987; Malle and Neubauer 1991; Moeller et al. 2001). This study opts to study one well-characterised aspect of impulsivity, response inhibition, given that its neuroanatomy is well understood, it is relatively easy to assess, provides robust functional activation measures (Garavan et al 1999) and, critically, it captures an aspect of impulsivity that has been shown to reveal performance and/or functional differences in previous tests of other drug using groups (Kaufman et al 2003; Fu et al 2008). The ability to inhibit prepotent behaviours is complemented by performance monitoring functions in that efficient control requires cognitive processes to identify when an error has occurred (Kiehl et al 2000; Hester et al 2004). Although evidence is inconsistent (Chamberlain and Sahakian, 2007), there is a longstanding association between reduced 5-HT (serotonin) neurotransmission and behavioural impulsivity (Tye, et al 1977; Soubrié et al 1986; Evenden et al 1999; Eagle et al 2009) and impaired monitoring (Risch and Nemeroff, 1992; Beats et al 1996; Elliott et al. 1997; Murphy et al. 2003).

The cognitive or neurobiological deficits that can be associated with recreational drug use remains unresolved. Even if not as harmful as harder drugs and if less likely to lead to dependence (Nutt et al., 2007), recreational use of drugs such as ecstasy and cannabis typically occurs at a younger age and by more people so any deleterious effects of these drugs, coupled with their possible role as gateway drugs to other harder drugs, may represent a significant epidemiological problem. In addition, accumulating evidence suggests that some neurocognitive deficits observed in users may pre-exist use (Tarter et al 2003; Dalley et al 2007; Verdejo-García et al 2008). Thus, observing neurocognitive

impairments in non-treatment seeking “recreational” users may give insights into the deficits that broadly characterise drug users insofar as there may be certain cognitive impairments relevant to all addictions.

The present study sought to investigate the neural basis of response inhibition and performance monitoring in current recreational drug users who use ecstasy as their primary drug of choice. An equal number of males and females were tested based on the evidence that current ecstasy use in females may lead to greater cognitive vulnerability (Topp et al 1999; Lynch et al 2002; Von Gersau et al 2004). More specifically, using a GO/NOGO event-related task we investigated Blood Oxygen Level-Dependent (BOLD) activation underlying response inhibition and performance monitoring in current recreational drug users who predominantly used ecstasy and healthy controls. Performance of GO/NOGO tasks places demands on behavioural inhibition processes, in that prepotent responses must be suppressed. Additionally the Impulsiveness Venturesomeness and Empathy questionnaire (IVE) was administered to provide a supplementary, self-report trait measure of impulsivity. The hypothesis was that polysubstance users who predominantly used ecstasy would report elevated measures of state and trait impulsivity and reveal dysregulated brain functioning during response inhibition and performance monitoring compared to healthy controls.

Methods and Materials

Participants

The drug-using group included 20 current users of ecstasy and the drug-naïve group was comprised of 20 participants with no history of illicit drug use. Participants were recruited by poster recruitment and by the snowballing method. Participants in the drug-naïve group were required to have never used any illicit substance. Participants in the drug-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 drug-using group were excluded if they used any other illicit drugs on more than ten occasions in their lifetime (or more than fifteen times if the substance had not been used in the five years that preceded the study) and were required to be abstinent of these drugs for a minimum period of 10 weeks prior to testing. Participants in both groups were also excluded if they had reported either past or present neurological or psychiatric problems. Given the fact that daily smoking of cannabis is part of the lifestyle of most club drug users (Daumann et al 2001), ecstasy users who were also cannabis users were not excluded from the study or required to abstain from smoking cannabis prior to participation. All drug-using participants who reported cannabis use (last use 0.5-12 days since last use), with the exception of one participant who had reported use three years prior to study participation, tested positive for cannabis. Drug users were requested to abstain from ecstasy for at least 48 hours prior to study participation. Given this abstinence period, all participants provided a negative urine sample for ecstasy. Additional urine analysis screening for methadone,

benzodiazepines, cocaine, opiates, barbiturates and tricyclic antidepressants (Cozart Rapid Urine, UK) revealed negative results in both 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 both the drug-using group and controls. The groups did not differ significantly in terms of verbal IQ as assessed by the National Adult Reading Test (NART), age, gender, years of education, alcohol or use of other illicit drugs with the expected exception of ecstasy and cannabis as specified in the selection criteria. The drug-using group self-reported higher Beck Depression Inventory (BDI) scores.

Experimental design

The GO/NOGO task

Participants completed a GO/NOGO task previously used for functional imaging of cocaine users (Kaufman et al., 2003) in which the letters X and Y were presented serially in an alternating pattern at 1 Hz and participants were required to make a button press response to each letter. Responses were to be withheld to NOGO stimuli: a NOGO occurred when the alternation was interrupted (e.g., the third stimulus in the train X-Y-Y-X-Y). The event-related design of this experiment allowed the NOGOs to be distributed unpredictably throughout the stimulus series. The inter-stimulus interval was 400 ms and each stimulus was presented for 600ms. Based on the work of Garavan et al. (2002) these

timing parameters were chosen to produce approximately an equal number of successful response inhibitions (STOPS) and errors of commission (ERRORS) in each subject. Participants were instructed to try to respond while the stimulus was on screen and responses and response speed were recorded. Prior to scanning participants completed a 60 second practice block of the task that contained six NOGO stimuli. During fMRI scanning, participants completed two runs that contained 450 GO stimuli and 50 NOGO stimuli, resulting in an average interval of ten seconds between NOGOs.

Psychometric measures

After scanning participants completed the Impulsiveness, Venturesomeness and Empathy Questionnaire (IVE). The IVE questionnaire contains 54 items requiring yes/no responses and consists of three scales assessing impulsiveness, venturesomeness and empathy (Eysenck et al 1991). Summary scores for impulsiveness and empathy each range from 0 to 19 and scores for venturesomeness range from 0 to 16 with higher scores indicating higher levels of the trait. Four participants from the ecstasy using group and one participant from the control group did not complete the IVE.

Imaging parameters

All scanning was conducted on a Philips Intera Achieva 3.0 Tesla MR system (Best, The Netherlands) equipped with a coil-mounted mirror that reflected a 640 x 480 pixel display, projected on a panel placed behind the subject's head outside the magnet. Imaging started with 31.5 seconds of standard scout images to adjust head positioning,

followed by a reference scan to resolve sensitivity variations. Imaging used a parallel SENSitivity Encoding (SENSE) approach (Pruessmaan et al. 1999) with reduction factor 2. 180 high-resolution T1-weighted anatomic MPRAGE axial images (FOV 230 mm, thickness 0.9 mm, voxel size 0.9 x 0.9 x 0.9) were then acquired (total duration 6 minutes), to allow subsequent activation localization and spatial normalization. Thirty-two non-contiguous (10% gap) 3.5 mm axial slices covering the entire brain were collected using a T2* weighted echo-planar imaging sequence (TE = 35 ms, TR = 2000 ms, FOV 224 mm, 64 x 64 mm matrix size in Fourier space).

Time-series analyses

The fMRI data were analysed using the AFNI software package (Cox, 1996). Time-series data were motion-corrected using 3D volume registration (least-squares alignment of three translational and three rotational parameters). Activation outside the brain was removed using edge detection algorithms. Deconvolution techniques calculated separate event-related haemodynamic response functions at 2s temporal resolution for successful response inhibitions (STOPS) and errors of commission (ERRORS). The haemodynamic response functions were then modelled voxelwise with a gamma-variate function using non-linear regression (Murphy and Garavan ,2005). An area-under-the-curve measure of the gamma-variate model was expressed as a percentage of the tonic baseline activity and served as the activation measure for the event-related responses. Activation maps were warped into a standard stereotaxic space (Talairach et al., 1998) and spatially blurred with a 4.2-mm full-width at half-maximum isotropic Gaussian filter after performing a second

edge detection on the skull-stripped brain. ERROR and STOP activation maps for both the drug-using group and drug-naïve controls were determined with one-sample t-tests against the null hypothesis of zero activation changes (i.e., no change relative to tonic task-related activity ($p \leq 0.001$)). In addition, voxelwise independent-samples t-tests comparing drug users and drug-naïve controls were performed separately for both ERROR and STOP activations. Significant voxels passed a voxelwise statistical threshold ($t(1,38) = 8.94$, $P \leq 0.005$) and were required to be part of a larger 286 μl cluster of contiguous significant voxels. Cluster-sizes for both the one-sample and the between-group t-tests were determined through Monte Carlo simulations and resulted in a 5% probability of a cluster surviving due to chance.

Statistical analysis

Behavioural data were analyzed with the statistical package SPSS (version 12). Independent-group t-tests tested for group differences on self-reported psychometric measures and GO/NOGO performance measures. All tests were two-tailed and criterion for significance was set at $p \leq 0.05$. To conduct an analysis of covariance (with BDI scores as the covariate), mean activation was calculated for each participant for the functionally-defined regions-of-interest identified by the between-group voxelwise contrasts. Separate ANCOVAs were performed for each region. In addition, separate 2 (group) x 2 (gender) ANCOVAs (with BDI scores as the covariate) were also conducted on self-reported psychometric measures, GO/NOGO performance measures, and on these region-of-interest activation measures. Within the drug-using group, Pearson's correlations

investigated relationships between behavioural performance, ecstasy use and brain activation.

Results

Behavioural results

Independent-group t-tests revealed that the groups did not differ on the impulsivity ($p \leq 0.5$), venturesomeness ($p \leq 0.4$), and empathy ($p \leq 0.6$) scales of the IVE nor did they differ on any GO/NOGO performance measures including % STOPS ($p \leq 0.5$), error of commission reaction times ($p \leq 0.6$), or GO reaction times ($p \leq 0.3$) (Table 2). No gender differences or gender x group interactions were observed for any of these measures.

Neuroimaging results

Separate task activation maps for each group are shown in Figure 1. For STOPS, prominent activation was observed in the right inferior frontal gyrus and, to lesser extents, dorsolateral and ventrolateral PFC and right parietal cortex. ERRORS exhibited robust activation in bilateral ACC, bilateral PFC, bilateral insula, bilateral temporal cortex, and right parietal cortex. Qualitatively, the activation patterns of the drug-using group appeared similar but larger than the controls. In confirmation of this pattern, group differences for STOPS from the voxelwise independent-groups t-tests were found in the right middle and inferior frontal gyri (centre-of-mass: 41, 33, 18), right middle frontal gyrus (45, 12, 34), and right inferior parietal lobule (42, -40, 45). In these areas,

activation was greater for drug-users. Similarly, greater ERROR activations in the users were evident in the right middle and inferior temporal gyri (53, -41, -10). On ERROR trials, controls showed significantly greater deactivation in the left medial frontal gyrus (0, 61, 1) and left posterior cingulate (-1, -47, 26) (see Figure 2 and Table 3). All significant group differences persisted even with the addition of the BDI covariate. In addition, no gender differences and no gender x group effects were found.

In the drug-using group, high frequency (number of times of ecstasy use) ($r = 0.48$, $p \leq 0.05$) and high consumption (number of ecstasy tablets) ($r = 0.46$, $p \leq 0.05$) in the month prior to testing correlated with activation in the posterior cingulate ERROR cluster. The positive correlations indicate that in these regions, which were deactivated in controls, there were smaller levels of deactivation (in fact, for many users, small levels of positive activation) in those users who had higher levels of recent use. Neither impulsivity from the IVE, behavioural performance from the GO/NOGO task, nor any drug use measure correlated with activation in any of the brain regions that revealed a group difference. Also impulsivity from the IVE did not correlate with behavioural performance from the GO/NOGO task.

Discussion

Successful response inhibition recruited the right fronto-parietal cortex, whereas error processing was associated with bilateral frontal, bilateral insula and anterior cingulate activity, consistent with previous results obtained using response inhibition tasks (Braver et al 2001; Menon et al 2001; Garavan et al 2002; Aron and Poldrack, 2006). The results of this study show that in the absence of performance deficits, current recreational drug users whose predominant drug of choice was ecstasy, demonstrate hyperactive brain function for both successful and unsuccessful inhibitions relative to well-matched controls. The lack of impairment in the ecstasy using group on GO/NOGO task performance is in agreement with other studies (Fox et al 2002; Gouzoulis-Mayfrank, et al 2003). Indeed, for brain imaging purposes the absence of performance differences can be advantageous enabling us to discount secondary performance-related effects (e.g., frustration) from confounding the group comparison (Murphy and Garavan, 2004). Instead, the hyperactivity of the drug users in the absence of performance differences indicates that inhibiting was more demanding requiring greater levels of neuronal involvement. The ability of the users to marshal additional resources to maintain levels of performance comparable to the controls may explain why previous studies have failed to detect impairment in inhibitory control in ecstasy users and suggests that their functional impairment is more subtle than seen, for example, with the same task in cocaine users (Kaufman et al., 2003). That said, another consideration is that our drug-using group may have been a particularly high-functioning group (note that estimated IQ

was well above average) so the evidence here of brain activation differences during cognitive control may still be noteworthy. With regards to trait impulsivity, no differences were observed between the drug-using group and controls on the IVE measures, a result that is consistent with some previous studies (Clark et al 2008) but not with others (Morgan et al., 1998; Parrott et al., 2000). The cause for these discrepant findings are uncertain and may reflect differences in sample-specific characteristics. Despite previous reports that females are particularly vulnerable to the deleterious effects of current ecstasy use (Topp et al 1999; Lynch et al 2002; von Gersau et al 2004) the present results revealed no effect of sex on the differences in brain function between the drug users and controls.

The drug-using group demonstrated hyperactive neural responses for STOPS in the right dorsolateral PFC (DLPFC), inferior frontal gyrus (IFG) and parietal lobule. A widespread network of brain regions is involved in response inhibition but the network of right prefrontal (especially right inferior frontal gyrus) and inferior parietal regions are thought central to response inhibition (Garavan et al 1999; Konishi et al 1999; Liddle et al 2001, Garavan et al 2002, Hester and Garavan, 2004; Chambers et al 2006; Li et al 2006b). The magnitude of activity in this network may reflect the demands a successful inhibition places on an individual. Consistent with this interpretation, Garavan et al. (2006) showed greater fronto-parietal activation in more absentminded healthy participants, Braet et al. (2009) showed greater fronto-parietal activation in adolescents relative to adults and Nielson et al. (2002) showed greater left prefrontal activation in older patients; in these studies, which used very similar tasks to the one used in this experiment, the between-

group activation differences in the absence of performance differences, were interpreted to reflect greater task difficulty. Therefore, the observation of ecstasy-related hyperactivity in this response-inhibition network in the absence of performance differences can plausibly be interpreted to indicate that greater demands were placed on this system in the users to maintain performance at levels comparable to the non-using controls.

Consistent with the frontal hyperactivity reported here, a previous fMRI study found that ecstasy users showed greater activation in PFC compared with non-drug-using controls during performance of an immediate and delayed working memory task (Moeller et al 2004). The present results may be partly related to a substantial body of work associating ecstasy with serotonergic frontal deficits (O'Hearn et al 1988; Wilson et al 1989; Fischer et al 1995; Hatzidimitriou et al 1999). Although at a conceptual level the 5-HT theory of impulsivity may represent an over-simplification (Clark et al 2008), altered 5-HT neurotransmission in the PFC has been associated with failures of inhibitory control (Leyton et al 2001; Clarke et al 2004; Liu et al 2004) with recent evidence implicating 5-HT in being able to wait to respond rather than being able to countermand a response that has already begun (Eagle et al., 2009). However, the current study contained no assessment of neurotransmitter levels and it is noteworthy that there is evidence suggesting that noradrenaline rather than 5-HT may be the key neurotransmitter underlying motor inhibition (Chamberlain and Sahakian, 2007).

During ERRORS the drug-using group demonstrated hyperactive neural responses in the left medial frontal gyrus, right middle temporal gyrus and left posterior cingulate and there were positive correlations between the posterior cingulate area and measures of ecstasy use. Notably, the users did not differ in the areas that are most often linked with error-related processes such as the anterior cingulate and insula (Hester et al 2004; Lerner et al 2009) and which have been associated with dopamine function (Cropley et al 2006;; Klein et al 2007; Jochman and Ullsperger 2008). As both the medial PFC and posterior cingulate are part of the default-mode network (regions that are typically deactivated during active task performance; Greicius et al., 2003), the reduced deactivation in these regions in users in contrast to controls suggests an impairment in users in turning off the default mode on their failed attempts to inhibit. Impaired performance on attention demanding tasks has previously been associated with failure to deactivate the default-mode circuitry in both normal and clinical groups (Lawrence et al 2003; Mc Kieran et al 2003; Buckner et al., 2008). There is also a growing literature implicating the PCC in addiction, specifically with regard to craving and it being a predictor of relapse (Brody et al., 2007; Egan et al., 2003; Franklin et al., 2007; Paulus et al., 2005; Small et al., 2001). The exact functional or psychological consequences of dysregulation in the PCC are unclear but it is possible that the self-referential processes thought to be subserved by the PCC that are heightened during craving may contribute background noise during cognitive task performance. Indeed, it is tempting to speculate, given the absence of group differences in performance, that this region may be a particularly sensitive marker of drug-related dysfunction.

Low correlations between self-report and behavioural measures of impulsivity are a common finding (Gerbing et al 1987; Morgan et al 1998; Wingrove and Bond 1998; Lijffijt et al 2004; 2004; Reynolds, et al 2006; Douglas, et al 2007). As we failed to find associations between response inhibition performance, brain activation and trait impulsivity, our results are consistent with the view that impulsivity is not a single construct, but is composed of multiple traits and dispositions that may be somewhat independent (e.g. Gerbling et al. 1987). Moreover, whereas questionnaire ratings indicate general behavioural tendencies across a range of situations and rely on a subjective evaluation of one's behaviour, laboratory tasks provide an objective measure of a specific component of impulsivity at a single point in time.

It should be noted that rather than testing abstinent users in whom persistent neurotoxic effects of ecstasy might be evaluated, the present assessment is of recreational drug users who primarily use ecstasy and who have differing periods of abstinence from ecstasy and other illicit drugs. A notable characteristic of this sample is that a large proportion of ecstasy participants tested positive for cannabis and some had also used ecstasy within two-three days prior to fMRI scanning. Negative subacute effects of MDMA on cognition and mood have been previously characterized (Parrott and Lasky, 1998). Amphetamines have been reported to cause toxicity (Berman et al., 2009) and some of the participants also used amphetamines up to a total of 15 times in their lifetime. A larger proportion of the drug users were nicotine smokers. We did not record if participants smoked nicotine on the day of testing but as participants were not requested to abstain from nicotine prior

to testing the potential influence of nicotine as a confounding factor cannot be eliminated. Consequently, the current results might best be interpreted as showing the neurocognitive functioning of current polydrug users, albeit users who primarily use ecstasy and cannabis, rather than necessarily demonstrating persistent neurotoxic effects of those drugs. Assessing the neurocognitive functioning of current users is of importance to understanding how drug use (moreover, the polydrug use that is representative of drug users) impacts on the daily functioning and decision making of users.

As these current polydrug users were recruited based on their ongoing regular use of ecstasy, it is plausible that ecstasy use or ecstasy use in combination with other drug use, may be the cause of the observed brain function dysregulation. Furthermore, although we have some evidence that the functional differences observed are related to current ecstasy consumption, we can not determine if current effects are attributed to ecstasy use or ecstasy use in combination with other drug use. Equally plausible, given the correlational nature of research on human drug users, is that these neural effects preceded drug use and may have placed individuals at risk for drug use. Impulsivity is a risk factor for drug use (Tarter et al 2003) and compromised monitoring of one's behaviour may also contribute to drug use (Garavan & Stout 2005; Hester et al 2009). Despite the evidence for impulse control deficits in regular ecstasy users being inconsistent, whether contributing to or arising from drug use, the present results provide evidence that recreational drug users who predominantly used ecstasy display dysregulation in brain regions subserving cognitive control and default mode processes, some of which echo observations in users dependent on drugs considered more addictive and damaging to health (Nutt et al., 2007)

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Figure 1. Sagittal sections showing regions activated for successful inhibitions (STOPS) and errors of commission (ERRORS) in the GO/NOGO task.

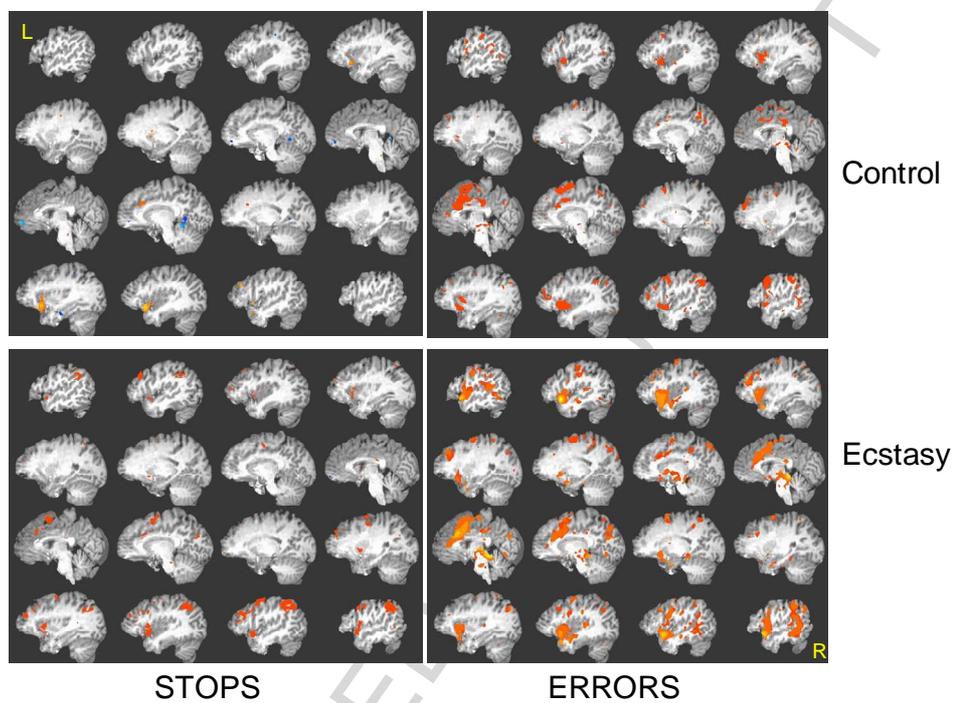
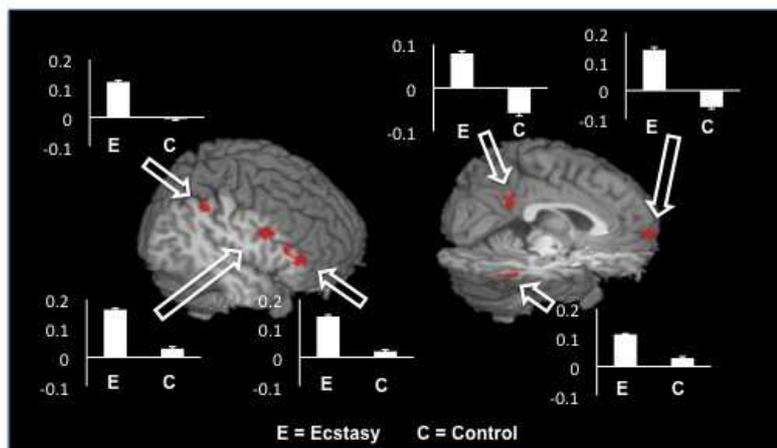


Figure 2. STOP and ERROR related brain activation for GO/NOGO task.



Significantly greater STOP-related activation in the drug-using group relative to controls was observed in the right middle and inferior frontal gyrus, right middle frontal gyrus, and right inferior parietal lobule. The drug-using group showed greater activation in the left medial frontal gyrus, right middle and inferior temporal gyrus, left posterior cingulate for ERRORS.

Table 1. Mean and SEM for ecstasy and control groups on demographics and drug use history.

	Ecstasy (n=20)	Controls (n=20)
Age	22.4±0.7	22.5±0.6
Years of education	15.8±0.5	16.9±0.6
Verbal intelligence score (NART)	122.1±1.1	123.3±0.9
Beck Depression Inventory II score	5.8±0.9	3.2±0.7*
Females/males	10/10	10/10
Ecstasy use in the last month (no. times)	2.3±0.4	0
Pills in last month (number)	10.7±2.7	0
Last ecstasy use (days)	16.17±2.5	0
Lifetime pills (number)	406.5±88.1	0
Pills in last year (number)	109.7±29.2	0
Years of cannabis use	6.8±0.7 (n=15)	0
Days of use in last month (number)	16.1±2.8 (n=15)	0
Joints in last month (number)	43.2±12.4 (n=15)	0
Last cannabis use (days)	102.5±99.1 (n=15)	0
Lifetime joints (number)	2479±732.1 (n=15)	0
Years of alcohol use	7.6±0.7	6.32±0.6
Alcohol use in the last month (no. days)	9.0±1.7	6.1±0.9
Average units of alcohol per week	14.4±2.1	10.6±0.9
Years of nicotine use	5.0±0.7 (n=14)	5.3±1.2(n= 6)
Years of amphetamine use	3.1±0.8 (n=11)	0
Last amphetamine use (days)	362.1±145.2 (n=11)	0
Amphetamine use (no. times)	6.3±1.7 (n=11)	0
Years of cocaine use	3.0±0.4 (n=17)	#
Last cocaine use (days)	152.3±55.4 (n=17)	0
Cocaine use (no. times)	9.8±1.2 (n=17)	0
Years of hallucinogen use	1.4±0.8 (n=7)	0
Last hallucinogen use (days)	640.7±264.2 (n=7)	0
Hallucinogenic use (no. times)	2.2±0.4 (n=7)	0
Ecstasy use in the last month (no. times)	2.3±0.4	0

*= $p < 0.05$ control versus ecstasy using group. # = on the day of testing one participant from the control group reported using 1 line of cocaine on 4 occasions (last use was 2 years prior to testing and when this participant was removed from the analysis the results remained unmodified). The only hallucinogen reported was LSD. Means are based on only those subjects reporting non-zero values for certain drug use. In these instances, the numbers of subjects reporting any use are given in parentheses.

Table 2. Psychometric and GO/NOGO response inhibition behavioural results.

	Ecstasy (n=16)	Control (n=19)
IVE		
Impulsivity	63±1	64±1
Venturesomeness	20±1	19±1
Empathy	24±1	23±1
GO/NOGO performance	(n=20)	(n=20)
% NOGO	52 ± 2	57± 2
EOC reaction times (ms)	303 ± 8	287 ± 6
GO reaction times (ms)	323 ± 10	308 ± 8

Table 3. Cerebral Foci for GO/NOGO group differences in activation.

Structure	Brodmann area	Hemisphere	Volume (μl)	centre of mass		
				X	Y	Z
		STOPS				
Middle and inferior frontal gyrus	46,10	R	1101	41	33	18
Middle frontal gyrus	9,8,6	R	488	45	12	34
Inferior parietal lobule	40	R	412	42	-40	45
		ERRORS				
Medial frontal gyrus	10	L	723	0	61	1
Middle temporal gyrus	20,37	R	406	53	-41	-10
Posterior cingulate	31, 23, 30	L	331	-1	-47	26