

Electrophysiological indices of response inhibition in human polydrug users

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Abstract

Previous research in ecstasy users suggests impairment of various executive functions. In general, the executive function of response inhibition appears unaffected by ecstasy use. Nonetheless, it remains a possibility that cognitive tasks alone are not sensitive enough to pick up subtle changes in function. The current study sought to investigate behavioural measures of response inhibition and their electrophysiological correlates in drug users. Twenty ecstasy polydrug users, 20 non-ecstasy polydrug users and 20 drug naïve controls were recruited. Participants completed questionnaires about their background drug use, sleep quality, fluid intelligence and mood state. Each individual also completed a Go/NoGo response inhibition task whilst electroencephalography (EEG) measures were recorded. Analysis of variance (ANOVA) revealed that there were no between-group differences on the behavioural measure of response inhibition. Multivariate analysis of variance (MANOVA) revealed no main effect of group across midline electrodes for the P3, N2 and P2 components. Univariate ANOVA revealed significant between-group differences in the P2 component with the ecstasy user group having a significantly higher mean amplitude than drug naïve controls at two midline frontal electrodes: at Fz and significantly higher mean amplitude than both control groups at FCz. The present study provides evidence of atypical early processing in ecstasy users that is suggestive of compensatory mechanisms ameliorating any behavioural differences.

Keywords

Ecstasy, memory, executive function

Introduction

Use of the recreational drug 3, 4- methylendioxyamphetamine (MDMA; ‘ecstasy’) has remained stable over recent years despite growing concern about long-term effects of the drug. The stability in use may reflect a decrease in purity and a rise in the use of comparable legal highs (non-illicit amphetamine analogues and psychedelics). However, recent media reports suggest that the purity of the drug is increasing and with the change in legal status of legal highs (according to UK law most ecstasy substitutes have been reclassified as class B illicit drugs), ecstasy remains a public health concern.

The acute psychological and physiological effects of ecstasy are primarily caused by serotonin (5HT) and dopamine agonism amongst other neurotransmitters (McDowell and Kleber, 1994). During acute regular use it may be expected that ecstasy causes downregulation of serotonin receptors as seen in animal models (e.g. Reneman et al., 2002). However, following periods of chronic use compensatory upregulation of 5-HT_{2A} receptors is seen in the human brain suggesting an attempt to maintain homeostasis after neurotoxicity (Di Iorio et al., 2012; Reneman et al., 2002; Urban et al., 2012). Such neurotoxicity has been observed in several animal studies (Molliver et al., 1990; Ricaurte et al., 1988), and in humans reductions in 5-HT, 5-hydroxyindoleacetic acid (5HIAA), tryptophan hydroxylase and loss of 5-HT reuptake sites and neuronal transporters are documented (Parrott, 2002). Research has observed 5-HT system impairments in currently abstinent ecstasy users (Gerra et al., 2000), with neuroendocrine alterations (responses to cortisol and prolactin) being attributed to use of MDMA. In addition, several studies have reported degradation of the serotonin system in abstinent users with decreased cortical serotonin binding compared to nonusers (Erritzoe et al., 2011; Kish et al., 2010; McCann et al.,

2008). Given the involvement of serotonin in the regulation of several physiological functions including sleep, mood and cognition, it is reasonable to postulate that depletion of serotonin in certain brain regions may account for ecstasy-related disturbances in mood and cognition (Montgomery et al., 2005a).

Areas that are involved in working memory such as the dorso-lateral prefrontal cortex are richly innervated with 5-HT receptors: therefore degradation to the serotonergic system via ecstasy use could lead to deficits in cognitive processes maintained by these forebrain structures. Significant deficits have been observed in ecstasy users compared to nonusers in components of working memory such as visuospatial working memory span (Wareing et al., 2004), access to semantic memory and memory updating (Fisk et al., 2004; Montgomery et al., 2005b). Furthermore, ecstasy users perform poorly in information processing tasks when cognitive demand is high (Wareing et al., 2000). It has been suggested (Cole et al., 2002) that sleep (among other possible lifestyle variables), or lack of it, may exacerbate or indeed be causal of cognitive deficits observed in ecstasy-using

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populations. Furthermore, several characteristics of sleep, such as sleep quality, length of sleep (hours) and related changes in alertness have been reported to be altered in ecstasy users relative to controls (Allen et al., 1993). However such deficits appear to have little mediating effect on ecstasy-related cognitive deficits (Montgomery et al., 2010) and more recently Blagrove et al. (2011) have found no evidence for ecstasy impairing the memory consolidation phase of sleep.

When looking at executive functioning in ecstasy users, some functions appear to be more affected than others, with the updating function of the executive being particularly susceptible to ecstasy use (Montgomery et al., 2005a; Montgomery and Fisk, 2008) along with access to long term memory (Montgomery et al., 2005a). Inhibitory control and set switching appear to be more robust to ecstasy-related deficits: however recent research in ecstasy users suggests that even in the absence of behavioural differences, ecstasy users may show electrophysiological differences related to task demands (Burgess et al., 2011). Such paradoxical effects can be seen in the implicit cognition literature where heavy drug users can show altered electrophysiological responses to drug stimuli in the absence of behavioural differences (Petit et al., 2012). Consequently, participants in previous studies reporting null results on behavioural measurements may not necessarily be exhibiting 'normal' functioning. The present study therefore sought to assess response inhibition in ecstasy users through behavioural and electrophysiological assessments of performance.

Inhibitory control, or the inhibition of prepotent or dominant responses, has been assessed in ecstasy users previously. The Stroop task has been used in several studies to observe whether ecstasy use affects inhibition performance (Back-Madruga et al., 2004; Gouzoulis-Mayfrank et al., 2000; Morgan et al., 2002), with all studies reporting no ecstasy-related impairment. Wareing et al. (2000) employed random letter generation to assess inhibition in ecstasy users and did observe performance deficits in ecstasy users compared to nonusers. However, further studies from the same laboratory (Fisk et al., 2004) did not replicate this. A review by Murphy et al. (2009) stipulated that the literature on inhibition in ecstasy users was unclear, although there is little evidence to suggest ecstasy-related impairments here. Furthermore, any perceived impairment is often obscured by confounding variables such as polydrug use and although the use of analysis of covariance (ANCOVA) and regression are usually employed to statistically control for this, the majority of findings in the literature need to be interpreted with some degree of caution. Previous studies using a cued Go/NoGo task with ecstasy users (e.g. Gouzoulis-Mayfrank et al., 2003), have observed little difference in performance on the task between nonusers, moderate users and heavy users. However, it has been suggested that 5-HT depletion, as well as impaired executive functions may play a role in inhibitory control (Morgan, 2006). One study that has been conducted on ecstasy users with minimal exposure to other drugs (Halpern et al., 2004) reported that heavy use of MDMA led to notable impairments in inhibition and impulsivity.

Although much of the research on behavioural tasks assessing inhibitory control in ecstasy users has provided inconclusive evidence, perhaps such cases where no differences have been observed can be attributed to compensatory mechanisms. Various mental strategies could be compensating for the more commonly-used areas for inhibitory control that result in undetectable differences behaviourally. This has been observed in cannabis users previously,

whereby in a task assessing spatial working memory, behavioural measures indicate that the processes involved are intact. However, analysis of regional brain activity using functional magnetic resonance imaging (fMRI) suggests that there is an increase in activation in regions usually involved in spatial working memory tasks as well as additional activation in regions not normally associated with this type of task (Kanayama et al., 2004). Similarly, Jager et al. (2006) observed that cannabis users showed alterations to left superior parietal cortex activity, from analysing fMRI data, despite equivalent performance to controls on a working memory task. Both of the preceding studies suggest that drug-related deficits in cognition could be compensated by differences in brain activity during performance.

Neuroimaging techniques such as electroencephalography (EEG) may be useful in providing a clearer indication of possible alterations of normal cognitive functioning. Indeed, such techniques are used in other clinical samples. For example, in patients with Alzheimer's disease, neuroimaging shows that patients exhibit increases in prefrontal activity in comparison to controls during executive function tasks. Saykin et al. (1998) observed that Alzheimer's patients displayed additional activation in frontal regions which they postulated reflects recruitment of additional resources from local and remote regions when conducting a semantic memory task. Moreover, Woodard et al. (1998) observed that on tasks that require rehearsing list information, Alzheimer's patients would display a shift in processing resources recruited from more anterior regions as cognitive load increases. This was interpreted as recruitment of additional resources due to increased demand on the frontal cortex. Compensatory reallocation in Alzheimer's disease patients was investigated further by Grady et al. (2003). Using positron emission tomography (PET) they observed that patients employed a unique network of resources in the DLPFC compared to controls, which they infer as being evidence for additional/compensatory neural mechanisms being recruited. Such resources facilitate performance by supplementing the degraded primary neuronal pathways involved in executive functioning.

In event related potential (ERP) research, cognitive impairment is associated with alterations to the P3 amplitude or latency, due to the P3 being involved in processing of stimuli. Due to the Go/NoGo task requiring continuous attention to the stimuli in order to respond to a stimulus (Go) or to withhold/inhibit a response (NoGo), it is useful for measuring processing and attentional capacity in ERPs (Smith et al., 2004). The P3 component, although a significant component in many cognitive tasks due to its involvement in attentional processing, does not appear to have a consistent role in response inhibition. This is possibly due to this component occurring relatively late in terms of the stages of processing and therefore perhaps not in the initial early inhibition processes. The N2 component is observed to be involved in inhibition as this component has been suggested to reflect stimulus discrimination (Ritter et al., 1982) and is therefore an important measure of response inhibition. Kok and colleagues (2004) suggest the N2 component shows greater amplitude in trials where inhibition of response is required (no go) than no inhibition (go) trials. Moreover amplitude of N2 is more prominent in unsuccessful inhibition trials. The N2 component is associated with errors (i.e. 'error negativity' or Ne), and is sensitive to monitoring errors. This has been suggested to be a product of activity in medial frontal regions such as the anterior cingulate (Bekker et al., 2005). The P2 wave can be observed at anterior and central sites, and elicits a larger response to simple target features that are relatively infrequent (Luck and

Hillyard, 1994). This component precedes the N2 and is suggested to be involved in the initial inhibition from further processing in target stimuli (Hansen and Hillyard, 1998).

EEG studies in ecstasy users

Differences between ecstasy users and controls have been observed in P3 components. Casco et al. (2005) observed a reduction in P3 amplitude in both heavy and moderate ecstasy user groups compared to controls in visual evoked potentials (VEPs) pertaining to a simple discrimination task, though no differences in latency were observed. However Mejias et al. (2005) report longer P3 latencies for detection of target stimuli in a visual odd-ball task, suggesting reduced cognitive processing. De Sola et al. (2008) assessed the relationship between cognitive function in ecstasy users and P3 ERPs. Here a more predictable difference between ecstasy users and healthy controls was observed with ecstasy users showing a negatively correlated latency in P3s and semantic word fluency and verbal memory. Furthermore, a reduced P3 amplitude was also observed in ecstasy polydrug users compared to non-drug controls and cannabis users, although this was non-significant. Although, the delayed latency in cognitive processing was consistent with other behavioural studies of ecstasy users, the P3 ERPs still fell within the normal range and thus failed to reflect electrophysiological differences in cognitive processing. Despite this, sub-clinical deficits are often observed so further investigation is warranted.

More recently, Burgess et al. (2011) looked at ERPs as evidence for selective impairment of verbal recollection in currently abstinent recreational MDMA/polydrug users. Interestingly, there appeared to be no significant differences between ecstasy users, polydrug controls and drug naïve controls on the behavioural tasks (memory tasks which involved recognition of words and faces). However, the ecstasy user group showed attenuation of late positivity over left parietal scalp sites, which is a component associated with the memory process of recollection. The finding of ecstasy users showing a durable abnormality in this ERP component exemplifies how EEG is a much more sensitive measure of cognitive impairment than behavioural measures alone. This point is further elucidated by Nulsen et al. (2011) wherein ecstasy users displayed alternative patterns of activity in ERPs compared to drug naïve and polydrug controls in short term and working memory tasks, despite no significant behavioural differences.

The aim of the current study was to observe whether there are any behavioural or electrophysiological differences between ecstasy users and controls in a task measuring inhibitory control (Go/NoGo). In view of the previous literature it is predicted that any behavioural differences will be negligible, however observable differences in components of the elicited ERPs are predicted in line with compensatory mechanisms. More specifically, it is envisaged that ecstasy polydrug users in particular will differ from both controls and non-ecstasy polydrug users. As such, this study aims to characterise the nature of ecstasy's effects on cognitive processes involved in inhibition of a response.

Method

Design

In all analyses, the between-groups factor was drug user group with three levels (ecstasy user, non-ecstasy polydrug user and

drug naïve controls). Univariate ANOVA was conducted on the behavioural data with the composite scores on the Go/NoGo (NoGo errors) as the dependent variable. ERP data was analysed using multivariate analysis of variance (MANOVA) with drug user group as the between-subjects factor and mean amplitude of the three ERP components at electrode sites Fz (frontal midline), FCz (frontal central midline), Cz (central midline), CPz (central posterior midline) and Pz (posterior midline) as the dependent variables.

Participants

Twenty ecstasy users (mean age=23.95 years, standard deviation (SD)=2.50, 10=male), 20 non-drug user controls (mean age=23.10 years, SD=2.94, 7=male) and 20 non-ecstasy drug user controls (mean age=22.58 years, SD=3.45, 9=male) were recruited via direct approach to university students, and the snowball technique (Solowij et al., 1992).

For inclusion in the study, participants had to be aged between 18–29 years and not have any neurological impairment. For inclusion in the ecstasy user group, participants had to have taken ecstasy/MDMA on five or more occasions. Indices of ecstasy use were as follows: total lifetime dose 177.65 tablets±301.73; mean amount used in the last 30 days 0.6 tablets±2.26, and frequency of use 0.24 times/week±0.42. Furthermore, for inclusion in both control groups participants must have never used ecstasy/MDMA, however all other illicit substances were permitted for the non-ecstasy poly drug user control group.

All participants were asked to abstain from consuming ecstasy for a minimum of seven days prior to testing and urine samples were collected upon arrival to the lab to be sent away for urinary analysis of metabolites, to ensure abstinence had occurred. Participants were also requested to abstain from use of other illicit drugs for a minimum of 24 h prior to participating and ideally seven days.

Materials

Several questionnaires were issued to participants upon entering the lab. These included a background drug use questionnaire, which provides the researcher with indices of drug use patterns and other lifestyle variables. In this questionnaire comprehensive details of ecstasy use as well as other illicit drug use are requested, such as first and last drug use, patterns of drug use, frequencies and doses over time. Using a method employed by Montgomery et al. (2005b), estimates of total lifetime drug use of each drug were calculated. Totals for last 30 days drug use as well as weekly drug use estimates were also calculated. This questionnaire also sought information about health, age, years of education and changes to mood and cognition amongst other lifestyle variables.

Measures of sleep quality

Several questionnaires investigating sleep quality and alertness were employed to investigate any possible relationship between sleep quality and cognition. These include a sleep quality questionnaire, exploring typical quantities of sleep (how many hours slept typically, how many hours over the last three nights) and level of quality of sleep. The Epworth Sleepiness Scale (ESS; Johns, 1991), explores the chances of dozing or falling asleep in

various situations. A high total score here is indicative of increased subjective daytime sleepiness. The Morningness-Eveningness Questionnaire (MEQ; Terman et al., 2001) is a self assessment of morningness-eveningness in human circadian rhythms (originally developed by Horne and Östberg, 1976). A high score on this questionnaire is indicative of a morning type person and a low score is indicative of an evening type person. Finally the Karolinska Sleepiness Scale (Akerstedt and Gillberg, 1990), is a self assessment of sleepiness at the current moment in time, therefore this can be administered at different time points of the experiment to assess sleepiness,

State mood

State anxiety, arousal and depression were measured using scales devised by Fisk and Warr (1996). Participants were required to rate on a five-point Likert scale from 1=not at all, to 5=extremely, how they were feeling at the time of testing. A high score on each subscale indicates increased hedonic tone/anxiety/arousal.

North American Space Agency-Task Load Index (NASA-TLX, Hart and Staveland, 1988)

This is a multi-dimensional scale, consisting of six sub-scales (mental demand, physical demand, temporal demand, personal performance rating, effort and frustration). Participants are required to place a mark on a 100 mm line, indicating where they perceive their demand to be on the scale. These are administered to observe whether there are any differences between ecstasy users and non users in demand perceived by the participant as it has been suggested that ecstasy users may be more susceptible to stress than nonusers (Wetherell et al., 2012).

Inhibitory control

The Go/NoGo task is frequently used in combination with EEG to assess inhibitory control (Gamma et al., 2005; Kok, 1986; Oddy and Barry, 2009). Here, in a simplified version of the task participants are required to 'Go' (press the space bar) when an X appears on the screen: however, they are to inhibit their response 'NoGo', when any other letter appears (W, Y or Z). The task is designed such that 'X' appears 75% of the time and the 'NoGo' letters appear only 25% of the time. This is so that the task builds up a pre-potent response to 'Go'. Furthermore, the first block of the task has 'X' appearing 100% of the time, again to build up a pre-potent/dominant response which participants are required to inhibit. The task therefore comprises of two blocks; a practise block with 60 'Go' trials, followed by an interval and then a larger main block whereby participants are required to attend to 240 trials (180 Go/60 NoGo) lasting a total of approximately 15 min. The task has an inter-trial interval of 1.5 sec and participants had an epoch of 2.5 sec from stimulus onset to respond. Participants were instructed to respond as quickly and as accurately as possible.

Equipment

EEG was recorded using a 64 channel Biosemi Ag-AgCl active-two electrode system (Biosemi B.V., Amsterdam, Netherlands)

with pin type electrodes mounted in a stretch-lycra headcap (Biosemi). Electrodes were positioned according to the international 10–20 system. Electrical activity was recorded from the following sites: frontal (FPz, FP1, FP2), anterior-frontal (AFz, AF3, AF4, AF7, AF8), frontal (Fz, F1, F2, F3, F4, F5, F6, F7, F8), frontocentral (FCz, FC1, FC2, FC3, FC4, FC5, FC6), central (Cz, C1, C2, C3, C4, C5, C6), temporal (FT7, FT8, T7, T8, TP7, TP8), parietocentral (CPz, CP1, CP2, CP3, CP4, CP5, CP6), parietal (Pz, P1, P2, P3, P4, P5, P6, P7, P8, P9, P10), occipitoparietal (POz, PO3, PO4, PO7, PO8) and occipital (Oz, O1, O2, Iz). Sigma electrolyte gel was used to ensure contact between scalp and electrodes. Vertical and horizontal electro-oculograms (EOGs) were recorded using bipolar, flat Ag-ACl electrodes positioned above and below the left eye as well as to the outer side of each eye. Data was digitised at a sampling rate of 512 Hz and no filters were applied online so that the data could be visually inspected for noise and offline filtering could be performed.

Procedure

Testing sessions commenced at 0930 or 1330, and equal numbers of participants from each condition were tested in the morning as were in the afternoon. Upon entering the laboratory, participants were given a brief description of the experiment and written consent was obtained. Following this, participants were required to give a urine sample. The urine sample was frozen at -25°C and later transported to the clinical laboratories for analysis. First, participants were required to fill out the battery of questionnaires whilst their head circumference and other details were measured, and an electrode cap and electrodes were fitted. The questionnaires were administered in the following order: Background drug use questionnaire, MEQ, sleep quality questionnaire, mood scale, ESS, Karolinska Sleepiness Scale (pre-test) and fluid intelligence was assessed using Raven's Progressive Matrices (Raven et al., 1998). Following completion of these questionnaires, providing the EEG setup was correct and actiview running, the computerised task was completed on a desktop computer running Inquisit version 3.0.6.0 (Millisecond software, 2011). The NASA-TLX questionnaire was completed after the Go/NoGo task. Upon completion of the tasks a final KSS (after) was administered. Finally participants were fully debriefed and paid £20 in store vouchers. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

EEG analysis

The EEG data was analysed using brain electrical source analysis (BESA) 5.3 (MEGIS software GmbH, Gräfelting, Germany). All recordings were visually analysed offline, using high and low pass filters of 0.1 Hz and 40 Hz respectively. Any channels judged to be bad (for example noisy data or many motion artefacts) were replaced by interpolation and all data were EOG-corrected using BESAs primary components analysis (PCA)-based algorithm. All trials judged to be bad after this point were discarded. EEG was segmented into epochs from -500 to 1000 ms from time of stimulus onset. Epochs were time-averaged by stimulus type so that ERPs for correctly and incorrectly identified stimuli in each condition of each task (e.g. correct 'Go' responses, correct 'NoGo' responses and incorrect 'NoGo'

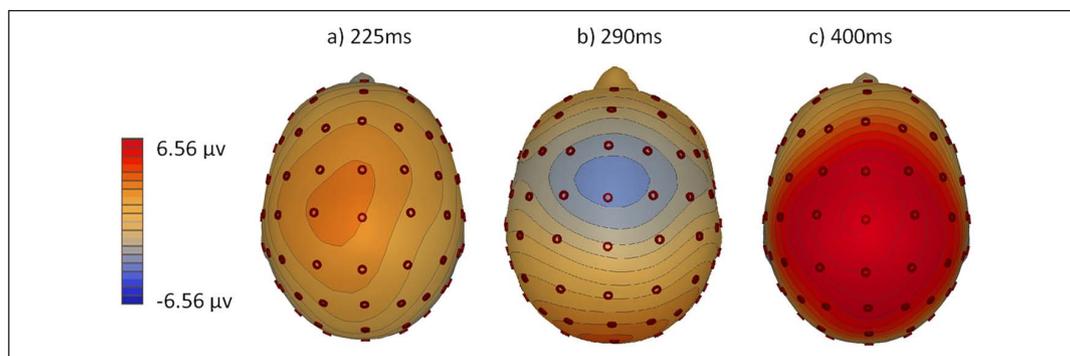


Figure 1. Topographies at midpoints for each component (P2, N2 and P3).

Shows the topographies for the central point of each component, note that this is from grand averages of each group combined. (a) shows a positivity in the P2 component that is clustered around the midline electrodes, (b) shows a negativity in N2 similarly in anterior midline electrodes and (c) shows a strong positivity in the P3 component that has a wide spread of activity that appears to peak at central electrodes.

responses in the Go/NoGo task) could be generated for each individual. Only ERPs for correct responses on the ‘NoGo’ condition were included in the subsequent analysis. There were 240 trials in the main block of the task, 60 of which were ‘NoGo’ trials. The mean number of good ‘NoGo’ trials retained for grand averaging per subject was 51.92 (average of 13.5% rejected trials), after rejecting incorrect trials (5%) and those containing artefacts (8.5%). Grand averages were made for each group (ecstasy user, polydrug user and drug naïve) on each task condition (correct ‘Go’ responses, correct ‘NoGo’ responses). The overall P3 response was defined as the mean amplitude between 352 and 452 ms. This window was centred on the positive peak latency and the duration was chosen due to this epoch containing the majority of positive activity for all conditions by observing topographic maps (see Figure 1). Midline electrode activity was obtained in this epoch from electrodes Fz, FCz, Cz, CPz and Pz, as much of the activity could be observed in these sites as well as these midline electrodes being commonly used for this task in the literature (Jonkman 2006; Kato et al., 2009). In addition further components were analysed for between-group differences, including the N2 and P2 components. The N2 (previously observed to be important in inhibitory control tasks of this type) of subjects in response to the inhibitory condition, was defined as the mean amplitude 260 and 330 ms, this epoch was based around the mean local negative peak at midline sites and encompassed the majority of negative activity over all three conditions. The P2 epoch was obtained from using a small, 50 ms epoch (200–250 ms) based around the positive peak from the grand averages of all conditions, directly preceding the N2.

Urinary analysis

Frozen urine samples were delivered to University Hospital Aintree (NHS) and were analysed using solid phase extraction (mixed mode phase) followed by reverse phase high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS) detection using both positive and negative ion multiple reaction monitoring (MRM). Urine specimens were tested for the synthetic cannabinoids (JWH-018, JWH-073, JWH-250, JWH-398, JWH-122, JWH-019, AM-694, WIN 48098 and WIN-55212-2), as well as the ‘designer’ drugs ‘mephedrone’, ‘methyline’ (bk-MDMA), or ‘butylone’ (bk-MBDB), or ‘methedrone’ (bk-PMMA), 1-benzylpiperazine, trifluoromethylphenylpiperazine (TFMPP),

meta-Chlorophenylpiperazine (mCPP), and methylenedioxypropylalderone (MDPV). In addition they were tested for a series of 12 piperazine compounds, 4 β -keto amphetamines, a series of 11 methcathinone compounds, 4-fluoroamphetamine, bupropion and the hallucinogenic amphetamines: DOB (‘bromo-STP’ or ‘brolamphetamine’), DOC and DOI and ‘traditional’ drugs of abuse: amphetamine(s) including MDMA, MDA. and MDEA, barbiturates, benzodiazepines, tetrahydrocannabinol (THC), and cannabinoids, buprenorphine, cocaine and metabolites, methadone and metabolites, opiates and opioids (morphine, codeine, dihydrocodeine, tramadol, d-propoxyphene, oxycodone and oxycodone), lysergic acid diethylamide (LSD), gammahydroxybutyrate (GHB), (and the lactone precursor), psilocybin, ketamine and methaqualone.

Statistical analysis

Data were analysed using MANOVA with drug user group as the between-subjects factor and the mean amplitudes at the five midline electrodes observed (Fz, FCz, Cz, CPz and Pz) as the dependent variables. Any significant effects between groups or electrodes were further analysed with a Tukey HSD test, to observe pairwise differences.

Results

Socio-demographic information about the participants, anxiety, depression and arousal scores from the mood scale and sleep measures are shown in Table 1. Indices of other drug and alcohol use are displayed in Table 2.

One way analysis of variance (ANOVA) revealed that there were no significant between-group differences on measures such as age, average hours sleep per night, total score on the ESS, MEQ total score, post test Karolinska Sleepiness Scale, levels of arousal, depression and anxiety or total score on Ravens Progressive Matrices. However there were between-group differences in the pre-testing Karolinska Sleepiness Scale (i.e. how sleepy the participants felt before the test battery) $F(2, 56)=3.78$, $p=0.03$, post-hoc Tukey’s test revealed that the ecstasy polydrug users felt significantly more sleepy prior to testing than the polydrug control group ($p=0.03$) but not the drug naïve control group.

Table 1. Indices of sleep quality, fluid intelligence and socio-demographic variables.

Males: <i>n</i> , %	Ecstasy users		Non-ecstasy drug users		Drug naïve controls	
	10 (50)		9 (45)		7 (35)	
	Mean	SD	Mean	SD	Mean	SD
Age	23.94	2.50	22.58	3.45	23.10	2.94
University degree; <i>n</i> (%)	14 (70)		12 (60)		11 (55)	
Employment status						
Student; <i>n</i> (%)	12 (60)		14 (70)		17 (85)	
Employed; <i>n</i> (%)	4 (20)		4 (20)		3 (15)	
Unemployed; <i>n</i> (%)	4 (20)		2 (10)		0 (0)	
Ravens Progressive Matrices (maximum 60)	48.68	5.96	48.35	5.83	51.35	5.01
Sleep; hours/night	7.13	1.91	7.8	1.39	7.05	1.16
ESS; score (maximum 24)	6.5	3.3	6.7	3.15	6.5	3.32
KSS before	5.05	1.93	3.75	1.48	4.79	1.23
KSS after	6.53	2.03	5.85	1.53	6.56	1.46
MEQ total	42.10	10.15	45.70	9.40	47.90	8.30
Mood anxiety	11.4	4.08	12.44	2.18	11.75	2.12
Mood depression	13.1	3.91	12.61	2.4	12.1	3.14
Mood arousal	19.7	4.54	20.5	3.68	20.1	3.02

ESS: Epworth Sleepiness Scale; KSS: Karolinska Sleepiness Scale; MEQ: Morningness-Eveningness Questionnaire; SD: standard deviation.

Table 2. Indices of other drug use.

	Ecstasy users			Non-ecstasy drug users			Drug naïve controls		
	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>
Cannabis									
Frequency (times/wk)	2.67	3.24	12	0.95	1.9	13	–	–	–
Last 30 days (joints)	32.77	53.75	15	6.09	15.34	17	–	–	–
Total use (joints)	5057.88	7504.30	16	1091.71	2531.65	19	–	–	–
Cocaine									
Frequency (times/wk)	0.15	0.14	11	0.27	0.34	2	–	–	–
Last 30 days (lines)	0.4	1.12	15	1.60	3.58	5	–	–	–
Total use (lines)	813.97	1940.19	16	107.30	208.43	5	–	–	–
Ketamine									
Frequency (times/wk)	0.26	0.42	5	0.02	–	1	–	–	–
Last 30 days use (grams)	1	2.65	9	–	–	–	–	–	–
Total use (grams)	31.26	70.61	11	1.13	1.62	3	–	–	–
Alcohol units per wk	15.33	15.29	20	10.53	8.37	20	9.93	11.58	20

SD: standard deviation.

Use of *t*-tests between the ecstasy user group and the polydrug non-ecstasy group revealed that the ecstasy user group had a significantly larger lifetime total of cannabis joints smoked (5057.88 ± 7504.30) than the non ecstasy drug users (1091.71 ± 531.65) $t(17.88)=2.02$, $p=0.03$ (Levene's test was significant so degrees of freedom have been adjusted accordingly). The ecstasy users had also smoked significantly more joints within the last 30 days (32.77 ± 53.75 compared to 6.09 ± 15.34) $t(16.01)=1.86$, $p=0.05$. There were however no differences between these two groups on other drug intake variables. However, as can be seen from the table, the ecstasy user group can be described as polydrug users.

Urinary analysis

As participants were asked to remain abstinent before attending the lab, relatively low levels of drug metabolites were found. Three ecstasy users' urine contained THC (mean 0.0083 mg/L ± 0.01185), Δ-9-THC (0.16 mg/L ± 0.18 mg/L), 11-hydroxy-Δ-9THC (0.003 mg/L ± 0.003). One ecstasy user's urine also contained 1-benzopiperazine (0.84 mg/L) and TFMPP (0.18 mg/L). One participant in the polydrug group had cannabis metabolites in their urine, specifically THC (0.001 mg/L), Δ-9-THC (0.41 mg/L) and 11-hydroxy-Δ-9THC (0.002 mg/L). As such, we re-ran all main analyses excluding the participants who had metabolites in their urine. This

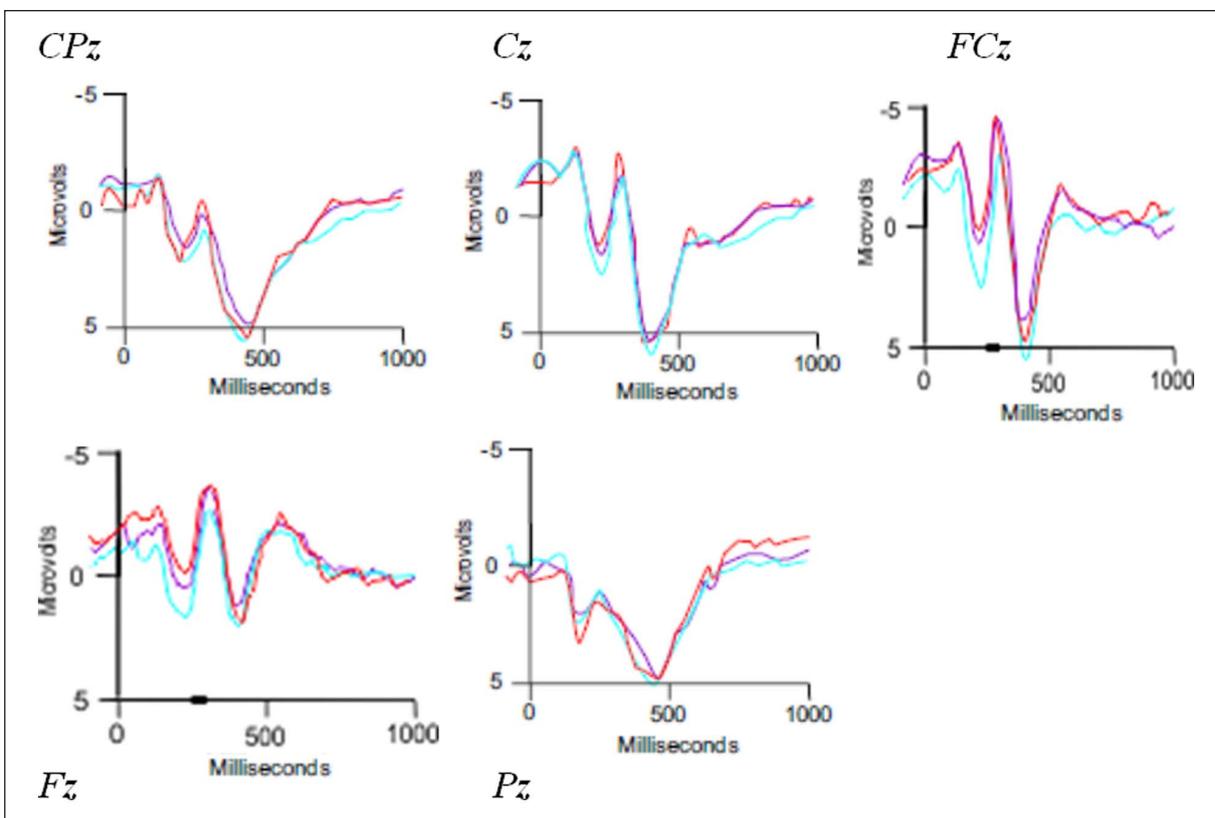


Figure 2. Grand average waveforms for the three groups across electrodes: CPz, Cz, FCz and Fz.(correct trials on Go/NoGo task). Depicts the waveforms from each electrode measured (negative plotted up). As such the time course of the various components can be observed. These waveforms are from grand averaged data from each user group. The significant differences of ecstasy users compared to drug naïve controls in the P2 component can be observed in Fz from the epoch of 200–250 ms (ecstasy users shown in blue, polydrug users in purple and drug naïve controls in red). Also the magnitude and time course of the significant differences in mean amp in the P2 component between ecstasy users and both other control groups can be observed in FCz. (ERP waveforms created using CorelDrawX5).

did not affect the significant and non-significant results and so the analyses reported below contain all participants.

Behavioural data analysis

The Go/NoGo task was programmed in Inquisit version 3.0.6.0 (Millisecond software, 2011) and was analysed using SPSS 17. Incorrect answers in each case were given a score of 0. Therefore an error count could be performed on each of the datasets. Further to this, mean reaction times were calculated for correct ‘Go’ responses. Reaction time was not an applicable measure for correct ‘NoGo’ responses. Univariate ANOVA revealed that there was no significant difference between groups in performance on this task $F(2,57)=1.15, p=0.33$. The mean ‘NoGo’ errors (i.e. responding to a letter other than an X that required no response/an inhibition of response) were used as the measure of performance in this case (Ecstasy users: 2.7 ± 1.95 , polydrug users: 3.4 ± 2.80 , drug naïve: 4.35 ± 4.92). However the mean ‘Go’ reaction time (ms) between groups was also non-significant $F(2,57)=0.35, p=0.71$ (Ecstasy users: 362.47 ± 42.60 , polydrug users; 372.60 ± 62.92 , drug naïve; 356.59 ± 74.08)

Post-task NASA TLX scores were analysed using a MANOVA. This revealed no overall between-group differences in task load $F(12,102)=0.52, p=0.90$, nor any between-group differences on the

individual sub-scales (Mental demand; $F(2,55)=0.15, p=0.86$, Physical demand; $F(2,55)=0.71, p=0.50$, Temporal demand; $F(2,55)=1.11, p=0.34$, Effort; $F(2,55)=0.09, p=0.92$, Performance; $F(2,55)=0.45, p=0.64$, Frustration; $F(2,55)=0.01, p=0.99$)

ERP analysis

The grand averages for each group (users, polydrug nonusers and drug naïve controls) can be observed at each electrode measured in Figure 2. Mean amplitudes for each condition and electrode are given in Table 3. Due to some unusable EEG data, one participant is excluded from statistical analysis on the EEG data, from the drug naïve group ($n=19$).

MANOVA of mean amplitudes at component P3 (352–452 ms) revealed no significant main effect of group on activity across the five electrodes measured $F(10,106)=0.35, p=0.96$. Moreover univariate tests yielded no significant differences at any of the individual electrode sites $p>0.05$ in all cases. Similarly multivariate analysis of variance of mean amplitudes at component N2 (260–330 ms) revealed no significant main effect of group on activity across the five electrodes measured $F(8,108)=0.78, p=0.62$, as well as the univariate tests yielding no significant between group differences at individual electrode sites $p>0.05$ in all cases.

Table 3. Mean amplitudes across components, for each electrode measured.

User group	CPz	Cz	FCz	Fz	Pz
P2					
Ecstasy user	2.17 (1.82)	1.94(2.69)	2.08 (2.15) ^a	1.43 (2.13)	1.45 (1.84)
Polydrug (non user)	1.3 (1.28)	1.16 (1.9)	0.29 (2.22)	0.40 (1.94)	1.43 (1.92)
Drug naïve	1.49 (3.24)	0.84 (2.1)	-0.14 (2.12)	-0.30 (1.79) ^b	1.64 (2.51)
N2					
Ecstasy user	1.38 (2.43)	-0.58 (3.60)	-1.92 (3.27)	-2.00 (2.14)	2.66 (1.72)
Polydrug (non user)	0.78 (2.67)	-0.82 (2.95)	-3.21 (3.33)	-2.87 (2.96)	2.16 (2.61)
Drug naïve	0.41 (3.50)	-1.42 (4.37)	-3.44 (4.33)	-3.12 (3.20)	2.16 (2.43)
P3					
Ecstasy user	4.93 (2.15)	5.04 (2.82)	4.06 (2.22)	1.05 (1.74)	4.29 (1.95)
Polydrug (non user)	4.07 (2.83)	4.56 (4.20)	2.91 (3.93)	0.49 (3.06)	3.76 (2.50)
Drug naïve	4.76 (2.65)	5.12 (2.77)	3.59 (3.23)	0.93 (3.12)	4.35 (2.10)

Table 3 shows the mean amplitude for each electrode on the three different ERP components for all three groups. Ecstasy users differed significantly from drug naïve controls at electrode site Fz. Furthermore the ecstasy users differed from polydrug users and drug naïve controls at electrode FCz (^a $p=0.03$ and $p=0.007$ respectively, ^b $p=0.02$).

MANOVA (with a full Bonferroni correction) for the P2 component (200–250ms) revealed the main effect on mean amplitudes was non-significant, $F(8,108)=1.62$, $p=0.13$, though there were a number of significant univariate effects at individual electrodes in line with our predictions. At electrode FCz $F(2,56)=5.81$, $p=0.005$ and also electrode Fz $F(2,56)=3.84$, $p=0.02$. Post-hoc Tukey's test revealed that the ecstasy users differed significantly from drug naïve controls at electrode site Fz ($p=0.02$). Furthermore the ecstasy users differed from polydrug users and drug naïve controls at electrode FCz ($p=0.03$ and $p=0.007$ respectively). Given the heavy use of cannabis in the ecstasy user group in particular, multiple regression analyses were conducted on the behavioural data, to observe whether level use of ecstasy (after controlling for cannabis use) was a predictor of amplitude at the electrodes Fz and FCz. In the first regression, amplitude at Fz was entered as the dependent variable; in the first step indices of cannabis use were entered as predictors (frequency of use, total lifetime dose, amount smoked in the last 30 days) and in the second step, the same indices of ecstasy use were entered as predictors. The overall regression model accounted for 13.8% of the variance in Fz amplitude. In the first step, cannabis use indices were not significant predictors (R^2 change=0.04, $F(3,55)=0.82$, $p=0.48$) ($\beta=-0.19$; 0.09; 0.06 for cannabis use indices respectively, $p>0.05$ in all cases). After controlling for cannabis use, total ecstasy use predicted an additional 10% of variance in Fz amplitude (R^2 change=0.10, $F(6,52)=0.91$, $p=0.49$) ($\beta=-0.01$; 0.01; 0.34 for ecstasy use indices respectively). While no individual indices of drug use emerged as significant predictors, amount of ecstasy used in the last 30 days approached significance $t(52)=1.68$, $p=0.09$. In the second regression, amplitude at FCz was entered as the dependent variable and predictors entered as above. The overall regression model accounted for 19.8% of the variance in FCz amplitude. In the first step, cannabis use indices were not significant predictors (R^2 change=0.06, $F(3,55)=1.09$, $p=0.36$) ($\beta=-0.05$; 0.19; 0.41 for cannabis use indices respectively as above, $p>0.05$ in all cases). After controlling for cannabis use, total ecstasy use predicted an additional 14.2% of variance in FCz amplitude (R^2 change=0.14, $F(6,52)=1.42$, $p=0.22$) ($\beta=-0.06$; 0.03; 0.42 for ecstasy use indices respectively). Amount of ecstasy used in the last 30 days

emerged as the only significant predictor of amplitude at FCz $t(52)=2.11$, $p=0.04$.

Discussion

The current study aimed to examine inhibitory processing in ecstasy polydrug users, with a task that focuses on the inhibition of a pre-potent response. The control groups did not differ from the ecstasy users on many of the background variables such as fluid intelligence, age, measures of sleep, levels of arousal, depression and anxiety. Nor did they differ on behavioural measures of performance on the inhibition task, such as number of failures to inhibit their response or reaction time in responding to targets that elicit a response ('Go'). Furthermore, the ecstasy users showed no differences in comparison to controls on perceived workload as measured by NASA-TLX.

Despite the lack of between-group differences on behavioural measures, there were differences in EEG measures suggestive of changes in attentional processes between the components involved in early inhibition processing (P2). Ecstasy users exhibited significantly higher mean amplitudes than both control groups at anterior midline site FCz and significantly higher amplitudes than drug-naïve controls at another anterior midline site Fz. It is interesting to observe such differences in the P2 component, given that it has been suggested that problems with early orienting or preparation may have consequences for later processing stages (Pliszka et al., 2000). Differences in this component have been observed previously in attention deficit hyperactivity disorder (ADHD) subjects (Johnstone et al., 2001; Lazzaro et al., 2001), with the ADHD subjects displaying greater amplitude in this component relative to controls. This has been interpreted as atypical inhibition of sensory input in ADHD subjects (Johnstone et al., 2001). In addition, research has shown that the P2 component is elevated in unexpected versus expected inhibition trials (Gajewski et al., 2008). Research has also investigated the P2 component in inhibitory control in high and low functional impulsives (i.e. individuals whose impulsivity may facilitate performance). High functional impulsives show an increase in P2 amplitude as a function of task demand (higher demand=increased amplitude)

whereas low functional impulsives do not (Fritzsche et al., 2011). Taken together, this suggests a number of explanations for the elevation of P2 in the present study. Firstly, ecstasy users have elevated impulsivity compared to nonusers and this impulsivity may be masking performance deficits. Fritzsche et al. (2011) suggest that this steeper P2 slope, as seen in the ecstasy-polydrug users, reflects earlier and more efficient evaluation of stimuli as a result of impulsivity. This seems a reasonable assumption given that elevated impulsivity has been noted in ecstasy users in previous research (e.g. Butler and Montgomery, 2004). The heightened P2 has been shown to be associated with stimulus evaluation and response (Gajewski et al., 2008). It is also worthy of note that Gajewski et al. (2008) only noticed the elevated P2 when they increased the demands of their task, which tentatively suggests that, in the present study, the task was more demanding for ecstasy users. Secondly, in line with the ADHD research cited above, the atypical early inhibitory processing displayed in the P2 ERP component in ecstasy users, could be due to recruitment of additional compensatory resources, similar to the increased activity in prefrontal areas associated with executive functioning deficits in Alzheimer's disease patients (Grady, et al., 2003; Saykin et al., 1998; Woodard et al., 1998). This proposal could also help explain the lack of observed behavioural differences on the task. Perhaps the recruitment of additional resources at this early stage in processing could offset any further waveform modulation at later processing stages. Particularly as this was a simplified Go/NoGo task, a temporal shift to the left in attention may not be surprising.

Although some previous studies report differences between ecstasy users and controls in the P3 component on a Go/NoGo task (Gamma et al., 2005), these have conceded that between-group differences were lower after age, education level and cannabis use were controlled for. Moreover, in Gamma et al.'s study they suggest that ecstasy users have lower P3 amplitudes in comparison to controls as a result of disinhibition. Conversely the present study observed that ecstasy users had a higher (although non-significant) P3 mean amplitude at the majority of midline electrodes compared to controls. Again, this suggests that the P2 related compensatory mechanisms might be obscuring any behavioural differences in a Go/NoGo where participants are instructed to answer as quickly and as accurately as possible (such as in the present study). Gamma et al. (2005) instructed participants to take their time and answer as accurately as possible. Perhaps this would lead to negligible behavioural differences, but could perhaps also contribute to differences in the ERP. For example, if a speeded response is not required, the lowered P3 amplitude reflects a generic cognitive deficiency in users, whereas if the task is speeded it requires instant recruitment of resources and also an increase in early processing. This may explain why the P2 was so prominent in the current ecstasy user sample.

The absence of between-group differences observed in the P3 component as well as the N2 component may be explained by the differences mentioned above. However both of these components were still clearly observed in all conditions of this task. Debates have arisen about the contribution of these two components in response inhibition. For example, although often cited as being reflections of inhibitory control (Kok, 1986; Kopp et al., 1996), the N2 has also been argued to have a role in conflict monitoring, rather than response inhibition (Donkers and Bostel, 2004; Nieuwenhuis et al., 2003). Furthermore, the P3

has been suggested to be insensitive to performance differences in inhibitory control and not necessarily involved in response inhibition (Falkenstein et al., 1999; Kopp et al., 1996). If this is the case then perhaps the task used in the current study, which was employed due to it tapping the executive function of inhibitory control only, would not highlight any differences in these components.

As with many other studies in this area, there are several limitations. Although the use of other drugs was controlled for, the ecstasy user group did smoke significantly more cannabis than the polydrug control group. Furthermore the ecstasy user group also reported consuming more cocaine than the polydrug control group. This is problematic for our results as cocaine has been shown to have strong associations with deficits in inhibitory control (Fillmore and Rush, 2002). In summary, perhaps it would be better to conclude that any effects were as a result of polydrug use. Indeed, aside from use in the last 30 days, ecstasy and cannabis use indices were equally poor predictors of mean amplitudes at the midline electrodes. In addition, a quasi-experimental design was employed and as such there may be some individual differences that belie the effects other than drug use. Many of these have been attempted to be controlled for, such as sleep quality, fluid intelligence and levels of arousal, depression and anxiety. Further to this, self-reported background drug use has been used to attain a description of quantity of drug use. However, this is problematic and recall here may not be completely accurate. Especially given the memory implications of drug use, however due to the legal status of the drug, this is the most appropriate method of investigating drug use and executive function, this method is also commonly used in the literature (Fox et al., 2001; Montgomery et al., 2005b, 2010). Purity and content of drugs consumed is also potentially problematic, though Parrott (2004) reported that ecstasy tablets collected from amnesty bins in nightclubs in the UK are approaching 100% purity. Additionally, biological analysis supports the presence of MDMA in both saliva samples of users (Parrott et al., 2008) and hair samples (Scholey et al., 2011), with the latter showing a very high correlation between self reports of usage and presence of MDMA metabolites in hair. Nevertheless, if this is incorrect and the purity is much lower, perhaps this raises additional concerns over the magnitude of cognitive effects observed (Montgomery et al., 2010).

The present study provides evidence for differences in electrophysiology as a result of ecstasy/polydrug use. Electrophysiological differences in early processing of response inhibition are suggestive of compensatory mechanisms employed to attenuate behavioural differences due to ecstasy related disturbances in normal processing of information.

Conflict of interest

The authors declare no conflict of interest.

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