ORIGINAL INVESTIGATION

ERP evidence suggests executive dysfunction in ecstasy polydrug users

C. A. Roberts · S. H. Fairclough · J. E. Fisk · F. Tames · C. Montgomery

Abstract

Background Deficits in executive functions such as access to semantic/long-term memory have been shown in ecstasy users in previous research. Equally, there have been many reports of equivocal findings in this area. The current study sought to further investigate behavioural and electro-physiological measures of this executive function in ecstasy users.

Method Twenty ecstasy–polydrug users, 20 non-ecstasy–polydrug users and 20 drug-naïve controls were recruited. Participants completed background questionnaires about their drug use, sleep quality, fluid intelligence and mood state. Each individual also completed a semantic retrieval task whilst 64 channel Electroencephalography (EEG) measures were recorded.

Results Analysis of Variance (ANOVA) revealed no between-group differences in behavioural performance on the task. Mixed ANOVA on event-related potential (ERP) components P2, N2 and P3 revealed significant between-group differences in the N2 component. Subsequent exploratory univariate ANOVAs on the N2 component revealed marginally significant between-group differences, generally showing greater negativity at occipito-parietal electrodes in ecstasy users compared to drug-naïve controls. Despite absence of behavioural differences, differences in N2 magnitude are evidence of abnormal executive functioning in ecstasy–polydrug users.

Keywords Ecstasy · *Cannabis* · Executive function

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Introduction

Recreational drug ecstasy/3,4-methylenedioxymethamphetamine (MDMA) is a potent indirect monoaminergic agonist, which is structurally similar to amphetamine and mescaline (Morgan 2000). Acute psychological and physiological effects include feelings of euphoria and empathy, increased energy, dilated pupils and tight jaw (trismus) (Davison and Parrott 1997) and are thought to result primarily from serotonin and dopamine agonism (McDowell and Kleber 1994). However "ecstasy" has been classed under the novel pharmacological category of entactogens owing to its unique psychoactive profile that can be differentiated from classic hallucinogens and stimulants (Morgan 2000).

Cognitive deficits have been reported amongst ecstasy users, and use is associated with working memory and executive functioning impairments (Fisk et al. 2004; Montgomery and Fisk 2008). Areas involved in working memory and executive function include the dorsolateral prefrontal cortex (DLPFC) and, dependent on nature of the task, hippocampus. These structures are densely innervated with 5HT neurons (Pazos et al. 1987). As such, degradation to integrity of this system via neurotoxicity or alternatively down-regulation from prolonged use of the drug may result in deficits in cognitive functions that these areas maintain. In addition to this, lack of sleep (amongst other possible lifestyle variables, such as heat and bioenergetic stress) has been suggested to exacerbate or even cause cognitive deficits observed in ecstasy-using populations (Cole et al. 2002). Furthermore, Allen et al. (1993) report that characteristics of sleep, such as sleep quality, quantity of hours and related changes in alertness are altered in ecstasy users relative to controls. More recently, Carhart-Harris et al. (2009) found that current and abstinent ecstasy users who reported little use of "other" drugs reported persistent abnormalities in

sleep patterns and quality. Nonetheless, deficits in memory have been observed to persist after controlling for sleep and other lifestyle variables (Montgomery et al. 2010).

The central executive of working memory has been suggested to comprise four discrete functions rather than being a unified construct (Miyake, et al. 2000). The initial three functions, monitoring and updating of working memory, inhibitory control and mental set shifting proposed by Miyake et al. (2000), were supplemented by a fourth component of "access" to semantic/long-term memory added by Fisk and Sharp (2004). This "access" component involves word fluency and efficiency of lexical access. Retrieval of words and semantics involves ability to access long-term memory store, and efficiency with which this can occur seems to be dependent on areas of the DLPFC (Stuss et al. 1998) as well as other subcortical networks (Jokeit et al. 1998). It may not be entirely surprising that word fluency requires long-term memory activation, and it has been observed that long-term recall is correlated with performance on word fluency tasks (Ruff et al. 1997).

Some studies have been conducted that assess access to semantic memory in ecstasy users using measures such as the Controlled Oral Word Association (COWA) task in which participants have 1 min to vocalise as many words beginning with F, A and S as possible (see Bhattachary and Powell 2001). Some studies using this measure have yielded deficits in ecstasy users compared to controls (Bhattachary and Powell 2001; Fox et al. 2001), whereas others report no such deficits (e.g. Halpern et al. 2004). However, as a written variant of the COWA, the Chicago Word Fluency Test appears to yield more consistent observable deficits in ecstasy users (Montgomery et al. 2005a, b; Montgomery et al. 2007). It remains a possibility that a verbal 1-min retrieval task, with no restrictions upon word type or length, is too simple to require involvement of the central executive and as such ecstasy users may not show any impairment on the COWA. It has been noted that ecstasy users have shown impairments on difficult aspects of tasks, yet appear unaffected on simple tasks that require relatively automatic processing (Fox et al. 2001). Consequently, further investigation of ecstasy-related deficits in access to semantic memory is required.

Neuroimaging techniques such as electroencephalography, positron electron tomography (PET) and functional magnetic resonance imaging (fMRI) are useful tools for this type of investigation. Firstly, it would be beneficial to observe neurophysiological correlates of behavioural deficits and the underlying mechanisms by which this executive function operates. In addition, due to necessity for neurophysiological techniques to reduce body movements and vocalisations so that data is not contaminated with noise, it would be advantageous to develop novel tasks to tap this

function as suggested by Murphy et al. (2009). Badre et al. (2005) used fMRI to observe the mechanisms by which semantic retrieval occurs in healthy controls. Participants were presented with a cue word and three target words on a screen for 3 s. Participants were required to either select a target (by using a keyboard) based on a global relation to the cue (i.e., no judgement made about specific features or dimensions of words such as shape, colour and semantics) or alternatively based on a specific semantic feature. Stimuli were matched for word length and frequency of presentation; furthermore, cue–target associative strength was varied. For example, a low semantic associative strength would have a cue word such as "detective" with targets "search, offer and pond" with "search" being the closest to "detective" semantically. An example of high associative strength would be "candle" with targets "flame, arena and goat" and here, it is clear that "candle" and "flame" are strongly associated in meaning and as such represent a high associative strength. Badre et al. (2005) posit that prefrontal cortex mechanisms mediate semantic retrieval and that the ventrolateral prefrontal cortex (VLPFC) and middle temporal cortex are sensitive to association strength.

Whitney et al. (2010) investigated the neuronal network involved in semantic retrieval and processing. Strength of semantic association with the cue word low vs. high was used as the manipulation. Transcranial magnetic stimulation (TMS) in healthy subjects was employed to disrupt processing in the inferior frontal gyrus (IFG) and the posterior middle temporal cortex. Disruption to both of these sites produced attenuation of effective processing of executively demanding processes; however, processing of cue–target stimuli with strong semantic association that are relatively automatic were unaffected by the disruption. It was concluded that there is a network of prefrontal and posterior temporal regions that underlie semantic control and may provide an explanation why ecstasy users may be unaffected in relatively simple semantic retrieval tasks, such as the COWA.

Indeed, electrophysiological measures such as EEG are more sensitive to detecting impairment than behavioural measures alone. For example, certain behavioural differences may be undetectable due to compensatory mechanisms that are employed to provide support for degraded primary mechanisms. This has been observed in patients with Alzheimer's disease (Rossi et al. 2004). Additionally, Saykin et al. (1998) investigated semantic retrieval in Alzheimer's disease patients with use of neuro-imaging and observed that they displayed additional activation in frontal regions compared to controls. This is suggestive of compensatory recruitment of additional resources in order to complete the tasks to a similar standard of performance to controls. Similarly, using fMRI, Kanayama et al. (2004) reported that *Cannabis* users displayed activation of

additional brain regions to those usually observed in a spatial working memory task using fMRI, despite behavioural measures providing no observable differences between them and controls. Here, results from behavioural measures would indicate that processes involved in spatial working memory were intact in *Cannabis* users, yet neuro-imaging data suggest recruitment of additional resources. Furthermore, Jager et al. (2006) have also reported alterations to left superior parietal cortex activity on working memory tasks in *Cannabis* users despite equivalent behavioural performance to controls on the task. Both studies highlight possibility of compensatory brain mechanisms underlying undetectable behavioural differences in working memory tasks in *Cannabis* users. We propose that similar mechanisms could operate in ecstasy users.

EEG is an electro-physiological technique with high temporal resolution that may be beneficial to use in combination with behavioural measures to assess any changes in brain function as a result of ecstasy use in semantic retrieval. Event-related potentials (ERPs) are ideal for investigating tasks that require executive control, as these tasks require rapid executive decisions that are less detectable with other neuro-imaging techniques. Burgess et al. (2011) observed differences between ecstasy users and controls in ERPs in a word recognition task. Ecstasy users showed an attenuation of a late positivity over left parietal scalp sites despite equivalent performance on the task. As such, this is suggested to be a durable abnormality in a specific ERP component associated with recollection in ecstasy users that may not have been detected with behavioural measures alone.

The P3 ERP is a positive spike in neuro-electric activity that occurs around 300 ms after stimulus onset. This component is thought to be involved in higher level cognitive processing and executive functioning. A diminished P3 potential is understood to reflect cognitive dysfunction. Casco et al. (2005) observed a diminished P3 response in a simple discrimination task in moderate and heavy ecstasy users compared to controls in a visually evoked potential study. Furthermore, Gamma et al. (2005) report reductions in the P3 amplitudes of ecstasy users, compared to controls in an inhibitory control (Go–NoGo) task. However, it is reported that this effect is diminished after controlling for age, educational level and *Cannabis* use. Indeed, the authors suggested that the diminished P3 response could be a polydrug effect given the amount of *Cannabis* use reported by ecstasy users in their sample. de Sola et al. (2008) conducted a battery of cognitive tests to investigate P3 differences between ecstasy users, *Cannabis* users and controls, and they found no significant between-group differences on these tasks in P3 latency or amplitude. However, there were significant correlations between P3 latency and lifetime *Cannabis* use, whereas Mejias et al. (2005) report

aberrations in the N2 component in ecstasy users compared to controls in a visual oddball task.

The current study aims to characterise the nature of MDMA's effects on cognitive processes involved in accessing semantic memory by using EEG measures during a semantic retrieval task similar to that used by Badre et al. (2005) and Whitney et al. (2010). It is hypothesised that behavioural differences will not be present in trials where there is high association between the cue and target words, but that differences will be observed with weaker semantic associations, as the weaker association condition will be more difficult, requiring induction of the central executive. Similarly, it is hypothesised that there will be differences in electro-physiological measures that reflect higher level processing (e.g., P3 and N2) whereby ecstasy users display aberrant electro-physiological behaviour compared to non-users.

Method

Design

In all analyses, a mixed design was used with a between-groups factor of drug user group with three levels (ecstasy user, non-ecstasy–polydrug user and drug-naïve controls) and associative strength (high vs. low) as a within-subjects factor. Mixed ANOVA was conducted on behavioural data with scores on semantic association tasks as dependent variable. ERP data was analysed using mixed ANOVA with drug user group as between-subjects factor and site of electrode (PO7, PO3, O1, OZ, POZ, PO8, PO4 and O2 for the N2 and P3 components and sites FZ, FCZ, FC1, FC2, CZ, C1 and C2 for the P2 component) as well as associative strength (high vs. low) as within-groups factors. Mean amplitudes at the three ERP components were the dependent variables. Where appropriate, significant main effects were further investigated using univariate ANOVA.

Participants

Twenty ecstasy users (mean age=23.95, SD=0.57, 10 male), 20 non-drug user controls (mean age=23.1, SD=0.66, seven male) and 20 non-ecstasy drug user controls (mean age=22.58, SD=0.79, nine male) were recruited via direct approach to university students and club goers. In terms of statistical power, with 20 participants in each of the three groups, the sample is sufficient to detect a difference between pairs of means of at least 1 standard deviation at alpha=0.05 and beta=0.20 (Hinkle et al. 1994). The additional control group of participants that have not used ecstasy previously, yet have used other illicit substances,

was recruited to address the issue of polydrug use as a potential cause for the cognitive deficits observed.

To avoid age-related deficits in working memory obscuring pharmacologically derived deficits, age range for inclusion was 18–29 years. Inclusion in the ecstasy user group required participants to have taken ecstasy/MDMA on five or more occasions over their lifetime (actual minimum=five ecstasy tablets). 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–polydrug user control group.

All participants were asked to abstain from consuming ecstasy for a minimum of 7 days prior to testing and urine samples were collected upon arrival to the lab for urinary analysis of all drug metabolites to confirm abstinence (after ingestion, MDMA is generally accepted to be detectable in urine for 1–3 days; this is the same for cocaine and amphetamines, with *Cannabis* being detectable for anything up to 95 days; Verstraete 2004). Participants were also requested to abstain from use of other illicit drugs for a minimum of 24 h prior to participating and ideally for 7 days.

Materials

Upon entering the lab, participants completed a background drug use questionnaire, which provides the researcher with indices of drug use patterns and other lifestyle variables. Comprehensive details of ecstasy use as well as other illicit drug use were 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. (2005a, b), estimates of total lifetime drug use of each drug were calculated. Totals for the last 30 days of drug use as well as weekly drug use estimates were also calculated. This questionnaire also sought information about health, age, years of education and perceived changes to mood and cognition, amongst other lifestyle variables.

Measures of sleep quality

Sleep quality and alertness were measured to investigate any possible relationship between sleep quality and cognition using the following questionnaires: 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 such as "sitting and reading" and "sitting quietly after lunch without alcohol", and is scored from 0=would *never* doze off to 3=*high* chance of dozing. A high total score here is indicative of increased subjective daytime sleepiness. The Morningness–Eveningness Questionnaire (MEQ)—self-assessment version (Terman et al. 2001) is a self-assessment of morningness–eveningness in human circadian rhythms (originally developed by Horne and Östberg (1976)), and 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 (ranging from 1=extremely alert to 9=extremely sleepy, fighting sleep, effort to stay awake); therefore, this can be administered at different time points of the experiment to assess sleepiness. As such, this was administered to participants pre- and post-task.

State mood

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

NASA-Task Load Index (Hart & Staveland 1998)

Finally, a questionnaire measuring subjective workload was given post-task. This is a multi-dimensional scale, consisting of six sub-scales (mental demand, physical demand, temporal demand, personal performance rating, effort and frustration). Participants were required to place a mark on a 100-mm line, indicating where they perceive their demand to be on the scale. These are taken to observe whether there are any differences between ecstasy users and non-users in perceived cognitive demand on the task. It has been reported that ecstasy users may be more susceptible to stress than non-users and may thus report increased cognitive effort (Wetherell et al. 2012).

Access to semantic memory

The executive function "access" was assessed using a semantic association task that is based around the tasks used by Whitney et al. (2010) and Badre et al. (2005), whereby two types of semantic judgement that differed in their level of difficulty (high association/low association) were used. In both difficulty levels, participants were presented with a cue word in the centre of a computer monitor followed by three target words, one which had a semantic association with the cue and two distracters. Participants had to decide which of the three target words had the strongest semantic association with the cue word. They selected their answer by pressing

one of three buttons on a response box that corresponded to their position on screen. They were either high association between cue and target words (e.g., candle–flame) or low association (e.g., detective–search). The low association judgement is deemed to be more difficult and require more processing than the relatively automatic high association semantic judgements. As such, the low association between cue and targets leads to a less obvious dissociation from distracters requiring recruitment of additional executive resources in the semantic network (Whitney et al. 2010). The stimuli used were matched for word length, frequency and cue–target association strength (Badre et al. 2005; Whitney et al. 2010) and were kindly provided by Whitney et al. The task consisted of a practise round followed by four blocks of 30 trials, with both high and low association trial types appearing in each block pseudo-randomly (15 of each in each block). The cue word was presented for 1 s in the centre of a computer screen. After this, the three target words appeared below aligned to the left, centre and right of the monitor. Participants were instructed to respond via pressing a button on the response box corresponding to the position of the target on the screen (left, centre and right). The targets remained on screen until a response was made or until the trial timed out (time out set to 8.5 s). An inter-trial interval of 2 s was employed. The task took around 20 min to complete. 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, the Netherlands) with pin type electrodes mounted in a stretch lycra headcap (Biosemi) and positioned according to the international 10–20 system. Neuro-electric activity was recorded from the following sites: frontal (FPz, FP1 and FP2), anterior–frontal (AFz, AF3, AF4, AF7 and AF8), frontal (Fz, F1, F2, F3, F4, F5, F6, F7 and F8), fronto-central (FCz, FC1, FC2, FC3, FC4, FC5 and FC6), central (Cz, C1, C2, C3, C4, C5 and C6), temporal (FT7, FT8, T7, T8, TP7 and TP8), parieto-central (CPz, CP1, CP2, CP3, CP4, CP5 and CP6), parietal (Pz, P1, P2, P3, P4, P5, P6, P7, P8, P9 and P10), occipito-parietal (POz, PO3, PO4, PO7 and PO8) and occipital (Oz, O1, O2 and Iz). Sigma electrolyte gel was used to ensure contact between scalp and electrodes. Vertical and horizontal electro-occulograms were recorded using bipolar, flat Ag–AСl 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 9:30 a.m or 1:30 p.m., and equal numbers of participants from each condition were tested in the morning and the afternoon. Upon entering the lab, participants were given a brief description of the experiment and written informed consent was obtained. Following this, participants gave a urine sample that was immediately frozen at −25 °C. Participants then completed 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, state mood, ESS, Karolinska sleepiness scale (before) and fluid intelligence was assessed using Raven's progressive matrices (Raven et al. 1998). Following completion of these questionnaires, the EEG setup was checked and, if necessary, modified. Participants then completed the computerised task on a desktop computer running Inquisit version 3.0.6.0 (Millisecond Software 2011). The NASA-TLX questionnaire was completed after the task as was the post-task Karolinska sleepiness scale. Finally, participants were fully debriefed and paid £20 in store vouchers. The study was approved by Liverpool John Moores University Research Ethics Committee and was administered in accordance with the ethical guidelines of the British Psychological Society.

EEG analysis

The EEG data was analysed using BESA 5.3 (MEGIS software GmbH, Gräfelfing, Germany). All recordings were visually analysed offline using high- and low-pass filters of 0.1 and 40 Hz, respectively. Any channels judged to be bad were replaced by interpolation and all data were Electrooculography (EOG) corrected using BESA's Principal Component Analysis (PCA) based algorithm. All trials judged to be bad after this point were discarded. EEG was segmented into epochs from −500 to 1,000 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 "high associations" and incorrect "high associations" and correct "low associations" and incorrect "low associations") could be generated for each individual. Only ERPs for correct responses were included in the subsequent analysis. There were 120 trials in total, and the mean number of good trials retained for grand averaging per subject was 109.66 (average of 8.6 % rejected trials) after rejecting incorrect trials (6.1 %) and those containing artefacts (2.5 %). Grand averages were made for each group (ecstasy user, polydrug user and drug naïve) on each condition (correct "high associations", correct "low associations"). The overall P3 response was defined as the mean amplitude between 280 and 350 ms for the low association
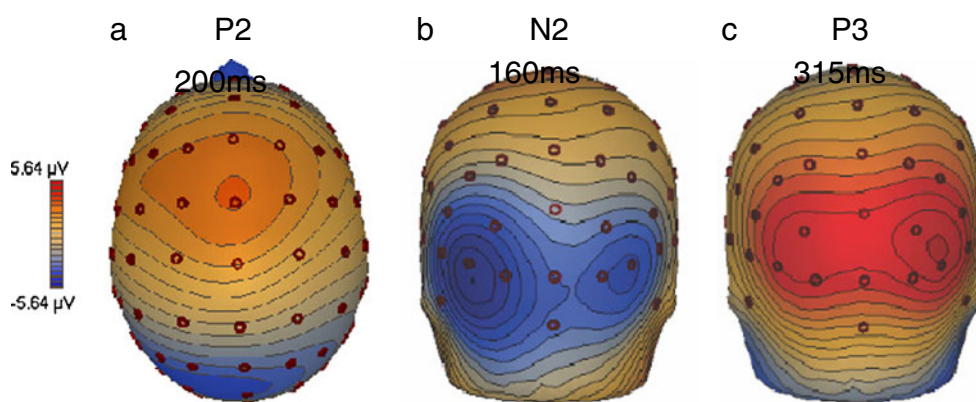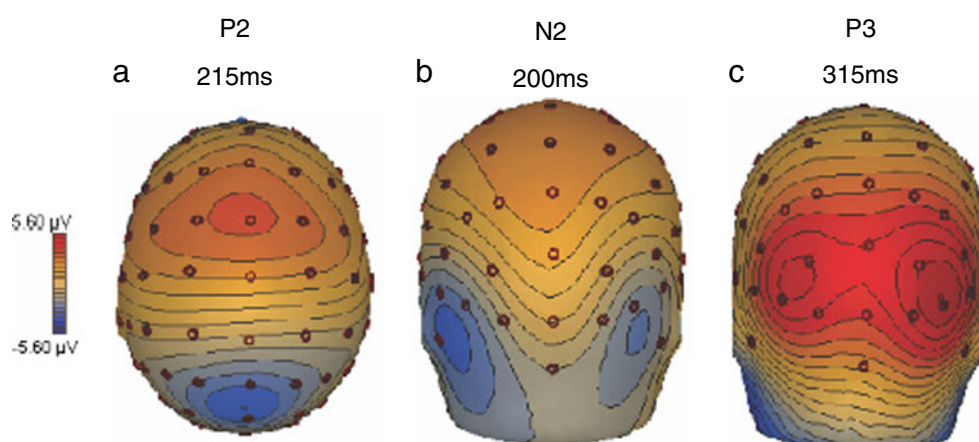
Fig. 1 Topographies for the central point of each component. Note that this is from grand averages of each group combined. **a** Topography of activity in the epoch specified for the P2 component. Note that this component has been isolated at an epoch where there is the most positivity displayed at midline/anterior electrodes. **b** A negativity in N2 notably around posterior and occipital electrodes. **c** Positivity in the P3 component similarly around posterior and occipital electrodes

condition and 250–350 ms for the high association condition. These time windows were centred on positive peak latency and duration was chosen due to this epoch containing majority of positive activity for all conditions by observing topographic maps (see Figs. 1 and 2). Electrode activity was analysed in this epoch from occipito-parietal and occipital electrodes PO7, PO3, O1, OZ, POZ, PO4, PO8 and O2, as the greatest amount of activity in the P3 component could be observed at these sites. Further, components were also analysed for between-group differences, including the N2 and P2 components. The N2 component was also the largest over occipito-parietal and occipital electrodes (PO7, PO3, O1, OZ, POZ, PO4, PO8 and O2) between 120–190 ms in the low association condition and 120–200 ms in the high association condition, and again, epochs were based around the mean local negative peak at these sites and encompassed the majority of negative activity over all three groups. The P2 component was most visible as a positive peak between 170 and 230 ms (for both low and high associations) at anterior and mid-line sites (FZ, FCZ, FC1, FC2, CZ, C1 and C2) and the mean amplitudes at these sites from the epochs based around the peaks from the grand averages of all conditions were analysed.

Urinary analysis

Frozen urine samples were delivered to University Hospitals Aintree and were analysed using solid-phase extraction (mixed-mode phase) followed by reverse-phase HPLC MS/MS detection using both positive and negative ion multiple reaction monitoring (MRM). Urine specimens have been tested for: 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 "designer" drugs "Mephedrone", bk-MDMA or "Methylone", bk-N-methyl-1,3-benzodioxolylbutanamine (MBDB) or "Butylone", bk-Para-Methoxymethamphetamine (PMMA) or "Methedrone", 1-benzylpiperazine, 3-Trifluoromethylphenylpiperazine (TFMPP), mCPP and Methylenedioxypyrovalerone (MDPV). Also tested for were a series of 12 piperazine compounds, four β-keto amphetamines, a series of 11 methcathinone compounds, 4-fluoroamphetamine, bupropion and the hallucinogenic amphetamines: DOB ("bromo-STP" or "Brolamphetamine"), DOC and DOI. Finally, "traditional" drugs of abuse: amphetamine(s) including MDMA, Methylenedioxyamphetamine (MDA)

Fig. 2 Topographies for central points of each component. Note that this is from grand averages of each group combined. **a** Topography of activity in the epoch specified for the P2 component. **b** A negativity in N2 notably around posterior and occipital electrodes. **c** Positivity in the P3 component similarly around posterior and occipital electrodes

Table 1 Indices of ecstasy use

Variable	Mean	SD
Total tablets	177.65	301.73
Last 30 days total	0.6	2.26
Frequency of use (times per week) (n=12)	0.24	0.42

and Methylenedioxyethylamphetamine (MDEA), barbiturates, benzodiazepines, THC and cannabinoids, buprenorphine, cocaine and metabolites, methadone and metabolites, opiates and opioids (morphine, codeine, dihydrocodeine, tramadol, d-propoxyphene, oxymorphone and oxycodone), LSD, GHB (and the lactone precursor), psilocybin, ketamine and methaqualone were tested for as well.

Results

Table 1 shows indices of ecstasy use from the ecstasy user group, including total lifetime dose (tablets), total number of tablets taken in the last 30 days and frequency of use (times per week). Participants' socio-demographic information, state mood scores from the mood adjective checklist and sleep measures are shown in Table 2, and indices of other drug and alcohol use are displayed in Table 3.

One-way 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 Raven's 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) ($F(2, 58)$=3.78, $p<0.05$), and planned comparison t tests revealed that the ecstasy user group felt significantly more sleepy prior to testing than the polydrug control group ($t(38)$=2.39, $p<0.05$), but not the drug-naïve control group $t(37)$=0.50, $p>0.05$.

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 joints smoked than the non-ecstasy drug users (5,057.88 compared to 1,091.71) ($t(17.88)$=2.02, $p<0.05$) (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 compared to 6.09) ($t(16.01)$=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 Table 3, the ecstasy user group can be described as polydrug users.

Urinary analysis

Metabolites detected in the urinary analysis are displayed in Table 4. Drug metabolites detected were restricted to cannabinoids, TFMPP and Benzylpiperazine (BZP) and were relatively low level. Exclusion of participants with cannabinoid metabolites in their urine did not change behavioural or

Table 2 Indices of sleep quality, fluid intelligence and socio-demographic variables

	Ecstasy users		Polydrug (non-ecstasy)		Drug-naïve controls	
Males: n, %	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: n (%)	14 (70)		12 (60)		11 (55)	
Employment status						
Student: n, (%)	12 (60)		14 (70)		17 (85)	
Employed: n (%)	4 (20)		4 (20)		3 (15)	
Unemployed: n (%)	4 (20)		2 (10)		0 (0)	
Raven's progressive matrices (maximum 60)	48.68	5.96	48.35	5.83	51.35	5.01
Sleep (h/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
State anxiety	11.4	4.08	12.44	2.18	11.75	2.12
State arousal	19.7	4.54	20.5	3.68	20.1	3.02
State depression	13.1	3.91	12.61	2.4	12.1	3.14

Table 3 Indices of drug use other than ecstasy

	Mean	SD	Number	Mean	SD	Number	Mean	SD	Number
Cannabis									
Frequency (times/week)	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)	5,057.88	7,504.30	16	1,091.71	2,531.65	19	–	–	–
Age at 1st use									
Cocaine									
Frequency (times/week)	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	1,940.19	16	107.30	208.43	5	–	–	–
Age at 1st use									
Ketamine									
Frequency (times/week)	0.26	0.42	5	0.02	–	1	–	–	–
Last 30 days use (g)	1	2.65	9	–	–	–	–	–	–
Total use (g)	31.26	70.61	11	1.13	1.62	3	–	–	–
Age at 1st use									
Alcohol units p/w	15.33	15.29	20	10.53	8.37	20	9.93	11.58	20

electro-physiological analyses so analyses reported include these participants.

Behavioural data analysis

The semantic association 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 and were not investigated any further for reaction time analysis. Mean reaction times were calculated for correct high association trials as well as correct low association trials. Reaction time data reduction involved excluding reaction times less than 200 ms and greater than 5,000 ms as these reaction times represent pre-emptive responding and a loss of concentration, respectively. Furthermore, individual trial reaction times that were more than 3 standard deviations above the individual mean were discarded. The mean percentage of outliers that were discarded from each group were ecstasy users 1.46 (±0.66),

polydrug users 1.42 (±1.05) and drug-naïve 1.71 (±0.92), and there were no between-group differences in amount of outliers ($F_{(2, 57)}=0.63$, $p>0.05$).

Performance on the semantic retrieval task was measured both in terms of number of errors made (incorrect responses) and reaction time. A mixed ANOVA was conducted with between-subjects factor of group and within-subjects factor of difficulty (high association and low association). Using error count as the dependent variable, there was no significant effect of difficulty ($F_{(1, 57)}=0.04$, $p>0.05$) (sphericity assumed), no main effect of group ($F_{(2, 57)}=1.56$, $p>0.05$) and no group× difficulty interaction ($F_{(2, 57)}=0.01$, $p>0.05$) (Table 5). Similarly, using reaction time as the dependent variable, no significant between-group differences were observed ($F_{(2, 57)}=0.07$ $p>0.05$). Difficulty and group×difficulty interactions were non-significant ($p>0.05$) in both cases (Table 5).

Post-task NASA-TLX scores were analysed using a multivariate analysis of variance (MANOVA). This revealed no overall between-group differences in perceived demand

Table 4 Amounts of various drug metabolites found in urine samples (mg/L)

		THC	Δ^9 THC	11-Hydroxy-Δ^9-THC	1-Benzylpiperazine	TFMPP
E user	N	3	3	3	1	1
	Mean	0.0083	0.16	0.003	0.84	0.18
	SD	0.01185	0.18286	0.00346	–	–
Polydrug	N	1	1	1	–	–
	Mean	0.001	0.41	0.0020	–	–
	SD	–	–	–	–	–
Drug naïve	N	–	–	–	–	–
	Mean	–	–	–	–	–
	SD	–	–	–	–	–

Table 5 Performance data (means and SDs of error count and reaction times) for all participants in both conditions

	Ecstasy users		Polydrug (non-ecstasy)		Drug naïve	
	Mean	SD	Mean	SD	Mean	SD
High association errors	4.00	2.34	4.60	2.78	5.25	2.77
Low association errors	4.10	2.57	4.60	2.09	5.35	2.92
High association RT (ms)	1,282.26	255.91	1,294.43	354.77	1,209.39	230.89
Low association RT (ms)	1,265.14	250.85	1,294.21	308.44	1,180.39	198.60

($F(12, 104)=0.94$, $p>0.05$) for Pillai's trace or any between-group differences on the individual sub-scales of their subjective perception of subjective workload (mental demand: $F(2, 56)=1.06$, $p>0.05$, physical demand: $F(2, 56)=0.10$, $p>0.05$, temporal demand: $F(2, 56)=1.56$, $p>0.05$, effort; $F(2, 56)=0.48$, $p>.05$, performance: $F(2, 56)=2.62$, $p>0.05$, frustration: $F(2, 56)=0.77$, $p>0.05$).

ERP analysis

The grand average waveforms for each group (users, polydrug non-users and drug-naïve controls) can be observed for electrodes PO7, PO3, O1, OZ, POZ, PO8,

PO4 and O2 in Fig. 3 (high association) and Fig. 4 (low association). Mean amplitudes for each condition and electrode are given in Table 6. Due to some unusable EEG data, one participant from the drug-naïve group ($n=19$) is excluded from statistical analysis on the EEG data.

A mixed ANOVA, with between-subjects factor of group and within-subjects factors of difficulty (high association and low association) and site (FZ, FCZ, FC1, FC2, CZ, C1 and C2), was conducted on the mean amplitudes across the epochs measured (170–230 ms in both conditions) for the P2 component. This revealed no main effect of difficulty ($F(1, 56)=0.32$, $p>0.05$), no difficulty × group

Fig. 3 Depicts the grand average waveforms for each user group from each electrode measured (for the N2 and P3 components) for the high association condition of the task. As such, the time course of the various components can be observed. (Ecstasy users are shown in *blue*, polydrug users in *green* and drug-naïve controls in *black*). Also, the magnitude and time course of the significant differences in mean amp in the N2 component (120–200 ms) between ecstasy users and drug-naïve controls can be observed in PO3, POz, PO4, PO8, Oz and O2. Epochs showing significant differences in the N2 component are emboldened in *black* on the *x* axis
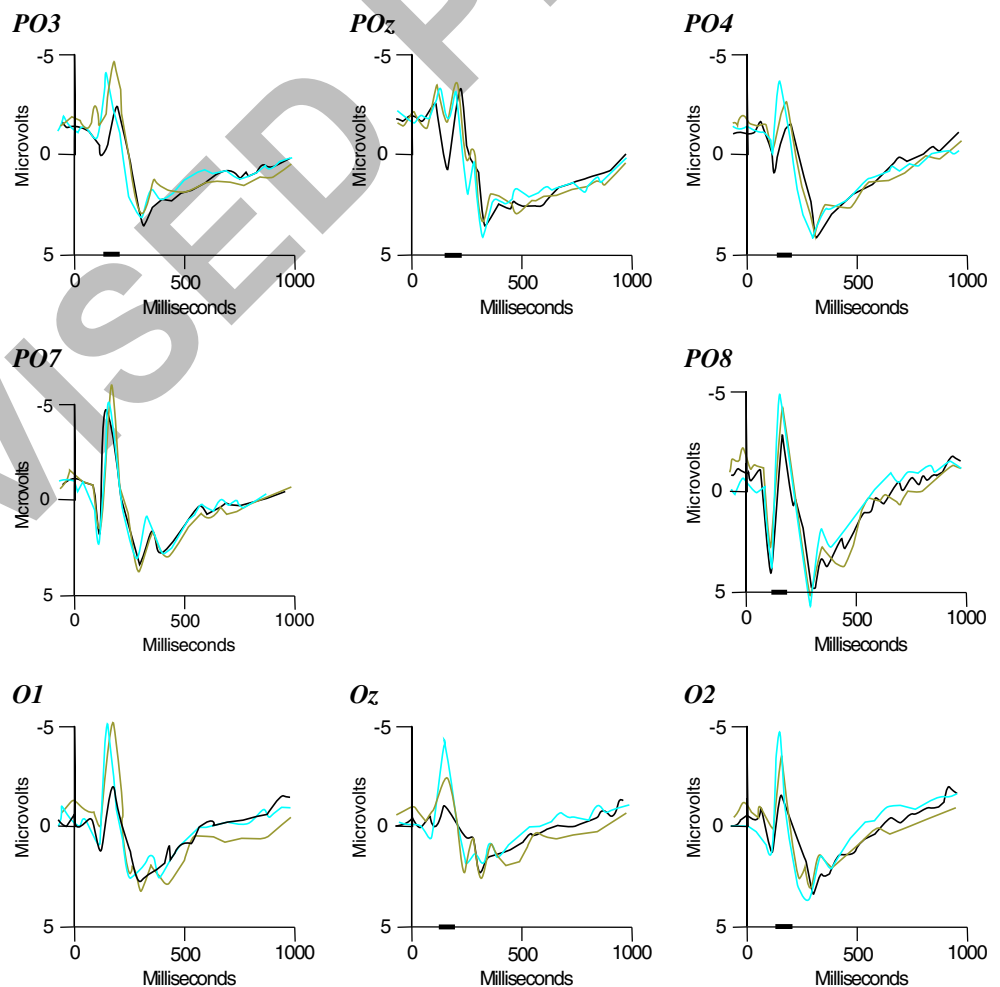
Fig. 4 The grand average waveforms for each user group (ecstasy user in *blue*, polydrug users in *green* and drug-naïve controls in *black*) from each electrode measured (for N2 and P3 components) for the low association condition of the task. The magnitude and time course of the significant differences in mean amp in the N2 component (120–190 ms) between ecstasy users and drug-naïve controls can be observed in PO4, PO8, O1, Oz and O2. Epochs showing significant differences are emboldened in *black* on the *x* axis
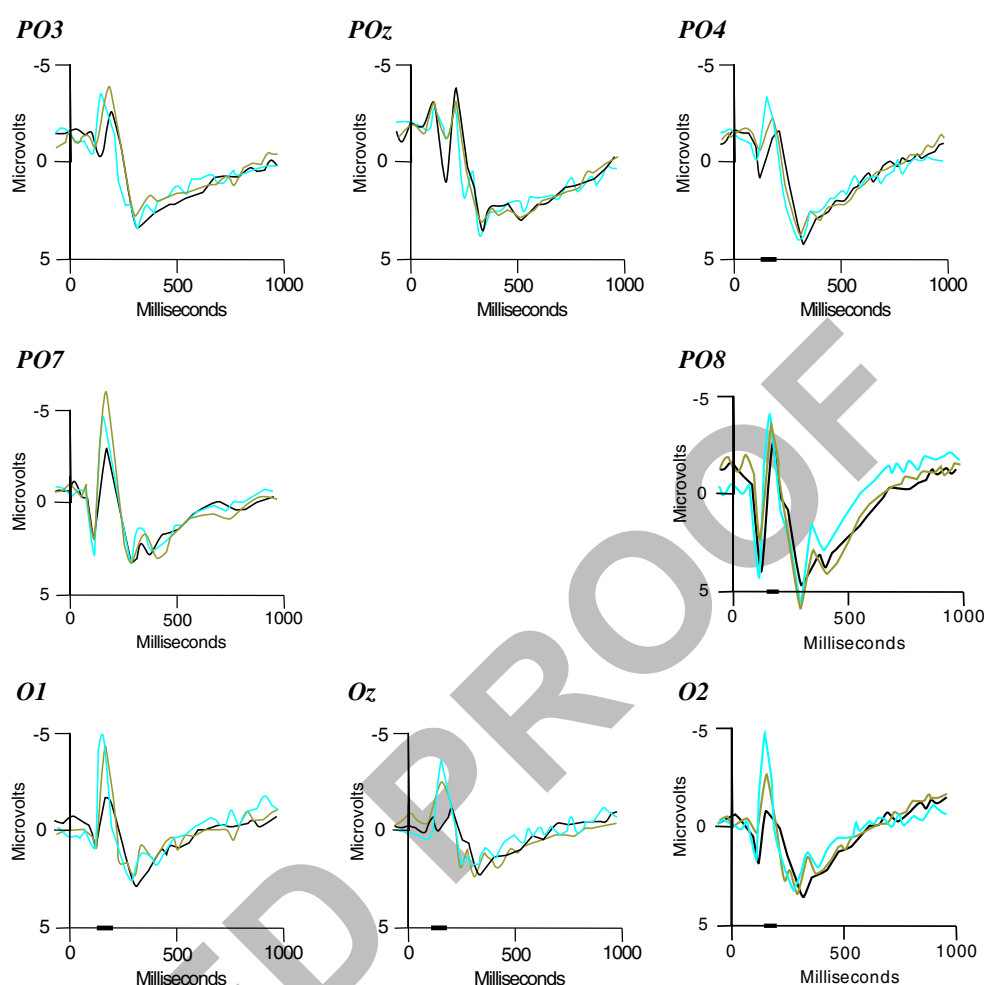
interaction ($F(2, 56)=0.35$, $p>0.05$), no main effect of site ($F(4.21, 236.03)=5.22$, $p>0.05$), no site×group interaction ($F(8.43, 236.03)=0.26$, $p>0.05$), no difficulty×site interaction ($F(4.85, 271.44)=0.51$, $p>0.05$) and no difficulty×site× group interaction ($F(9.69, 271.44)=0.48$, $p>0.05$ (degrees of freedom adjusted in line with Greenhouse–Geisser statistic in all cases). Between-group differences were also non-significant ($F(2, 56)=1.68$, $p>0.05$).

A mixed ANOVA, with between-subjects factor of group and within-subjects factors of difficulty (high association and low association) and site (PO7, PO3, O1, OZ, POZ, PO4, PO8 and O2) for the mean amplitudes across the epochs measured (120–190 ms in the low association condition, 120–200 ms in the high association condition) on the N2 component revealed no main effect of difficulty ($F(1, 56)=1.05$, $p>0.05$), no difficulty×group interaction ($F(2, 56)=0.04$, $p>0.05$), no main effect of site ($F(3.82, 213.92)=6.37$, $p>0.05$), no site×group interaction ($F(7.64, 213.92)=1.10$, $p>0.05$), no difficulty×site interaction ($F(4.78, 267.40)=0.81$, $p>0.05$) and no difficulty by site× group interaction ($F(9.55, 267.40)=0.73$, $p>0.05$) (degrees of freedom adjusted in line with Greenhouse–Geisser statistic in all cases). Between-group differences approached

significance ($F(2, 56)=2.78$, $p=0.07$). In line with a priori predictions and to further explore this trend on the N2 component, Helmert contrasts were performed. The Helmert contrasts revealed a significant difference between the ecstasy–polydrug user group and the drug-naïve participants (contrast estimate=−2.10, $p<0.05$). Consequently, univariate ANOVA was conducted between drug-naïve participants and ecstasy–polydrug users alone, with amplitude at each site as the dependent variable to explore the significant contrast. In the low association condition, significant differences were observed at electrode site O1 ($F(1,37)=3.37$, $p<0.05$), site OZ ($F(1,37)=3.41$, $p<0.05$), PO8 ($F(1,37)=6.32$, $p<0.01$), PO4 ($F(1,37)=3.42$, $p<0.05$) and O2 ($F(1,37)=7.02$, $p<0.01$). In the high association condition, significant differences were observed at site PO3 ($F(1,37)=3.62$, $p<0.05$), OZ ($F(1,37)=5.05$, $p<0.01$), POZ ($F(1,37)=2.83$, $p<0.05$), PO8 ($F(1,37)=5.56$, $p<0.01$), PO4 ($F(1,37)=2.84$, $p<0.05$) and O2 ($F(1,37)=4.17$, $p<0.05$). In all cases, ecstasy users showed greater negativity than drug-naïve controls (Table 6).

A mixed ANOVA, with between-subjects factor of group and within-subjects factors of difficulty (high association and low association) and site (PO7, PO3, O1, OZ, POZ,

Table 6 Mean amplitudes across components for each electrode measured

User group	P3 high association							
	PO7	PO3	O1	Oz	POz	PO8	PO4	O2
Ecstasy user (20)	2.95 (4.02)	3.94 (2.42)	2.76 (3.01)	1.60 (3.24)	4.19 (2.34)	4.40 (3.23)	4.94 (2.99)	3.31 (3.59)
Polydrug (20)	4.12 (2.83)	2.97 (2.57)	3.52 (4.60)	3.04 (3.40)	3.28 (2.27)	5.72 (3.78)	4.05 (3.27)	3.32 (3.32)
Drug naïve (19)	3.62 (3.19)	3.92 (2.39)	2.84 (3.17)	2.13 (3.14)	3.42 (2.56)	5.35 (3.40)	4.00 (2.21)	3.27 (2.75)
	P3 low association							
Ecstasy user (20)	3.48 (3.74)	4.60 (2.74)	2.32 (3.57)	1.79 (2.90)	4.46 (2.40)	3.78 (2.92)	4.98 (3.33)	2.97 (3.39)
Polydrug (20)	4.16 (3.29)	3.44 (3.16)	2.27 (4.40)	2.70 (2.85)	3.89 (2.26)	5.92 (4.61)	4.41 (3.67)	3.14 (3.90)
Drug naïve (19)	4.32 (3.42)	4.40 (2.64)*	3.08 (3.46)	2.22 (3.21)	3.93 (2.80)	6.07 (3.32)	4.54 (2.69)	3.78 (2.92)
	N2 high association							
Ecstasy user (20)	−1.66 (3.41)	−1.32 (3.55)	−2.19 (3.53)	−2.51 (3.45)	−0.70 (4.01)	−1.41 (3.20)	−1.04 (3.69)	−2.17 (4.12)
Polydrug (20)	−2.06 (4.57)	−2.37 (2.90)*	−2.41 (4.36)	−0.59 (4.19)	−0.58 (2.42)	−0.09 (4.11)	−0.44 (2.57)	−1.15 (3.44)
Drug naïve (19)	−0.58 (3.11)	0.67 (2.95) *	−0.36 (3.43)	0.09 (3.78)	1.22 (3.03)	1.12 (3.50)	0.82 (3.19)	0.33 (3.51)
	N2 low association							
Ecstasy user (20)	−1.40 (3.55)	−0.95 (3.76)	−2.76 (4.19)	−1.98 (3.57)	−0.17 (3.62)	−1.56 (3.53)*	−1.01 (3.67)	−2.40 (3.75)*
Polydrug (20)	−1.69 (4.69)	−1.55 (3.15)	−2.11 (4.47)	−1.09 (3.43)	−0.28 (2.16)	−0.22 (4.02)	−0.29 (1.91)	−0.10 (3.71)
Drug naïve (19)	0.01 (3.67)	0.65 (2.97)	−0.33 (4.07)	−0.99 (3.62)	1.55 (2.91)	1.30 (3.58)*	0.91 (2.73)	0.67 (3.48)*
	P2 high association							
	Fz	FCz	FC1	FC2	Cz	C1	C2	
Ecstasy user (20)	0.55 (2.15)	1.49 (2.04)	1.15 (1.79)	0.86 (2.09)	1.91 (1.48)	0.89 (2.13)	0.77 (1.53)	
Polydrug (20)	1.07 (1.98)	1.85 (1.54)	1.28 (1.52)	1.05 (1.87)	1.53 (1.73)	0.87 (1.87)	0.40 (1.64)	
Drug naïve (19)	−0.10 (2.43)	0.78 (2.43)	0.61 (1.45)	0.03 (2.75)	0.59 (2.78)	0.22 (2.03)	−0.22 (2.72)	
	P2 low association							
Ecstasy user (20)	0.87 (2.59)	1.64 (2.39)	1.33 (2.54)	0.83 (2.75)	1.55 (1.97)	1.06 (1.45)	0.93 (1.40)	
Polydrug (20)	0.51 (1.42)	1.72 (1.62)	1.49 (2.81)	0.98 (1.74)	1.38 (1.77)	0.88 (1.99)	0.62 (1.79)	
Drug naïve (19)	0.14 (1.90)	0.72 (2.16)	0.54 (1.98)	0.41 (1.79)	0.81 (2.41)	0.39 (2.22)	0.54 (1.97)	

*Denote significant main effects at $p < .05$

PO4, PO8 and O2) on the P3 component for the mean amplitudes across the epochs measured (280–350 ms in the low association condition, 250–350 ms in the high association condition) revealed no main effect of difficulty ($F_{(1, 56)} = 0.71$, $p > 0.05$), no difficulty × group interaction ($F_{(2, 56)} = 0.60$, $p > 0.05$), no main effect of site ($F_{(4.18, 233.99)} = 13.97$, $p > 0.05$), no difficulty × site interaction ($F_{(3.42, 191.64)} = 1.56$, $p > 0.05$) and no difficulty by site × group interaction ($F_{(6.84, 191.64)} = 0.61$, $p > 0.05$). However, there was a significant site × user group interaction ($F_{(8.36, 233.99)} = 1.65$, $p \leq 0.05$) (degrees of freedom adjusted with Greenhouse–Geisser statistic in all cases). There were no significant between-group effects ($F_{(2, 56)} = 0.74$, $p > 0.05$), so these were not investigated further. To further explore the site × user group interaction, a series of univariate ANOVAs were run with group as the between-groups variable and amplitude at the various sites as the dependent variable. This yielded no significant differences between the three groups and no significant post hoc comparisons ($p > 0.05$ in all cases).

Discussion

The current study investigated the executive function of access to semantic memory and its behavioural and electro-physiological correlates. Background variables such as fluid intelligence, age, measures of sleep, level of arousal, depression and anxiety showed no significant differences between the three groups. There were no behavioural differences between groups in terms of number of errors on task and reaction time to correct responses. Furthermore, ecstasy users did not differ significantly to the control groups with respect to subjective mental workload.

The electro-physiological data provide support for abnormal executive functioning in ecstasy–polydrug users. In the N2 component, although there were no main effects of difficulty or site, or any interactions with these and group, or difficulty by site by group, there were between-group trends that warranted further exploration. In the low association condition of the task, ecstasy users displayed a significantly larger negativity in the N2 (120–200 ms) component

compared to drug-naïve controls in occipital electrode sites O1, O2 and OZ and occipito-parietal electrode sites PO8 and PO4 compared to drug-naïve controls (Fig. 4), although non-ecstasy–polydrug users did not differ from either group.

The supposedly easier "high association" condition showed significant differences in negativity at the N2 component in ecstasy users compared to drug-naïve controls at occipital electrode sites OZ and O2 as well as occipito-parietal sites PO2, PO3, PO4 and PO8 (Fig. 3). Components that reflect positivities (P2 and P3) showed no main effects of difficulty or site, or any interactions with these and group, or difficulty by site by group (except in P3 where there was a site×group interaction) and there were no between-group differences. Thus, these components are less informative about access to semantic memory in ecstasy users. However, the group difference in the N2 component does provide some interesting points to consider.

The N2 component has been reported as having a source in the anterior cingulate cortex (Bekker et al. 2005; Nieuwenhuis et al. 2003; Van Veen and Carter 2002) and to reflect neural processes engaged during conflict monitoring, thus being increased in high conflict trials (Yeung and Cohne 2006), for example, when incongruence between targets and cues/distracters elicits a conflict of response in a Stroop task (Kopp et al. 1996). Firstly, considering why the N2 was more pronounced in ecstasy users compared to drug-naïve controls in those trials where there was a lower semantic association between target and cue words, it is possible that at this level of processing, the ecstasy users required the recruitment of additional resources in order to access the semantic network of long-term memory compared to drug-naïve controls. Previous research has provided evidence that ecstasy users' performance can be more greatly impaired under higher task difficulty. For example, Montgomery et al. (2005a, b) observed a decline in performance in a word fluency task when more rules were imposed, suggesting that deficits are more prominent in tasks that place more demand on the central executive. Moreover, given that participants reported no perceived differences in cognitive effort on the NASA-TLX, it is possible that compensatory cognitive processing at neurological sites is correcting for deficits in executive function to eradicate behavioural differences and other research reporting null results, with respect to performance, may reflect similar reallocation of cognitive resources. This aspect of the results was in line with our predictions.

However, ecstasy users also displayed greater negativity compared to drug-naïve controls in the high association condition of the task, suggesting perhaps that controlled processing, in general, is impaired regardless of task difficulty. It is generally accepted (Jefferies et al. 2004; Rosell et al. 2001; Shiffrin and Schneider 1977) that information

processing involves two modes of processing: automatic and controlled. Controlled processing, unlike automatic processing, involves selectively and consciously attending to a stimulus, suggesting that controlled processing involves higher level mental processes. As such, automatic processing is proposed to rely on long-term memory, whilst controlled processing loads more on working memory (Jefferies et al. 2004), suggesting separable neural substrates. Indeed, Rosell et al. (2001) used fMRI to investigate differences in effortful and automatic processing in a similar lexical decision priming experiment and found that distinct sub-regions of the anterior cingulate cortex showed activation dependent on the processing type involved. The N2 component in a semantic classification task was argued to reflect controlled processing by Ritter et al. (1982). Perhaps any early automatic processing (such as that observed in the P2 component) is unaffected by drug use, whereas such higher level controlled processes are more affected. Indeed, perhaps the N2 is the earliest stage at which controlled processing is detectable, and recruitment of additional resources at this stage could offset any further modulation of the waveform in later components such as the P3. Consequently, whilst we hypothesised that controlled processing and recruitment of the central executive would be elicited only in the low association condition, based on the results, it is likely that the task was demanding enough to recruit executive resources in both conditions.

Whilst the above discusses possible N2-related differences in access to semantic memory, it is indeed possible that the N2 in the present study reflects changes in other cognitive processes additional to semantic access (See Folstein and van Petten 2008, for review). The N2 in the present study was prominent in more posterior electrodes that Suwazono et al. (2000) suggest is reflective of increased attention demands in the visual cortex required for stimulus processing. In this study, posterior N2 was eliminated by eliminating target novelty (i.e., making targets completely predictable). Moreover, Luck and Hillyard (1994) investigated sub-components of the N2 component using visual search tasks. It was found that the bilateral posterior N2 as seen in the present study was related to visual search and target probability, with an increased posterior N2 when participants could not predict a target before presentation. Taken together, this provides tentative evidence that in the present study, the posterior N2 may reflect increased demands on visual search and maintenance of visual representations, with greater negativity in ecstasy–polydrug users, showing that they require increased attentional resources for this.

As with most studies on cognitive deficits relating to ecstasy use, there are some limitations that necessitate a degree of caution when interpreting the data. For example,

despite controlling for the use of other drugs, by introducing a polydrug control group (namely, *Cannabis* users) that had never taken ecstasy, the ecstasy users in this study smoked significantly more *Cannabis* that the polydrug group. The ecstasy user group also reported consuming more cocaine than the polydrug group. As such, any observed differences could still be attributed to the use of these other drugs or, indeed, a synergistic effect of concomitant use of other drugs. Perhaps any effects here could be better described as a result of polydrug use, especially given that ecstasy users, although showing greater negativities in the N2 in both conditions of the task compared to drug-naïve controls were not significantly different to polydrug controls.

Studies that employ quasi-experimental designs cannot exclude the chance that individual differences may belie any observable effect other than drug use. We attempted to control for many of these individual differences, such as sleep quality, fluid intelligence and levels of arousal, depression and anxiety. Another limitation lies in self-reports of background drug use, which may not be complete and accurate due to problematic recall of drug users. However, this is the most appropriate method of investigating drug use and executive function, given the legal status of the drug. Moreover, this method is commonly used in the literature (Fox et al. 2001; Montgomery et al. 2005a, b; Montgomery et al. 2010). Purity of the ecstasy tablets consumed as well as cocaine purity and *Cannabis* strength are all questionable and cannot be guaranteed. However, Parrott (2004) reported that the ecstasy tablets collected from amnesty bins in nightclubs in the UK was approaching 100 % purity. If this is incorrect, however, and purity is, in fact, much lower, perhaps this raises additional concerns about the cognitive effects observed (Montgomery et al. 2010).

The present study provides evidence for changes in electro-physiology in ecstasy/polydrug users. Durable abnormalities of the N2 component observed over occipital and occipito-parietal sites of drug users compared to drug-naïve controls is suggestive of compensatory mechanisms or re-allocation of cognitive resources that are deployed to attenuate any observable behavioural differences caused by ecstasy-related disturbances to traditional processing of semantic information and allocation of attention during visual search.

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