Electrophysiological evidence of atypical processing underlying mental set shifting in ecstasy

polydrug and polydrug users.

Running Head: Switching set in ecstasy and polydrug users.

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Abstract

Executive functioning deficits are reported in ecstasy users. However research into mental set switching has been equivocal, with behavioural studies suggesting the function is preserved. The current study sought to address the issue of switching deficits in ecstasy users by combining behavioural performance with electrophysiological correlates (EEG). Twenty ecstasy polydrug users, 20 non-ecstasy polydrug users and 20 drug naive controls were recruited. Participants completed questionnaires about their drug use, sleep quality, fluid intelligence and current mood state. Each participant completed a mental set switching task (the number-letter task) whilst EEG measures were recorded. ANOVA revealed no between group differences on performance of the task, however a regression suggested that ecstasy use was a significant predictor for performance, after controlling for cannabis use. Mixed ANOVA revealed a significant effect of group on the P3, with significant differences between both drug groups and naives. There was also an interaction between electrode and group on the P2 component, with ecstasy users differing from both other groups. On the P3 component the results suggest a reduction in positivity at parieto-occipital electrodes for drug users compared to controls. Furthermore a significant increase in negativity in ecstasy users compared to control groups could be observed in several occipito-parietal electrodes at an N2 component as well as observable atypicalities in early processing (P2) displayed by ecstasy users and polydrug controls. The present study provides evidence of atypical processing of attentional shifting in ecstasy and polydrug users. Deficits in this executive function could reflect cognitive inflexibility and paucity of rapid behavioural adjustment, which may be problematic in real world situations.

Conflict of interest.

The authors, Mr Roberts, Professor Fisk, Professor Fairclough, Professor McGlone and Dr Montgomery, declare no conflict of interest.

1. Introduction

Mental set switching is the ability to switch attention between task types, whereby a switch between tasks is associated with a performance cost, either in accuracy or time, compared to completing two tasks in succession (Jersild, 1927). Switching reflects cognitive flexibility and is one of the core executive functions outlined in Miyake *et al.'s* (2000) framework. Executive functions are the mechanisms which underpin the dynamics of human cognition (Miyake *et al.,* 2000) and as such alterations to switching ability may have implications for tasks undertaken in daily life. In ecstasy ("MDMA") users, research in switching is equivocal (Fox *et al*., 2001; Fox *et al.,* 2002). However tasks used do not always solely assess switching (Fisk and Sharp, 2004). The Wisconsin Card Sort Task (WCST) has been employed frequently in ecstasy users to assess switching (Renemann *et al.,* 2006**;** Thomasius *et al.*, 2003) yielding no ecstasy related deficits. The number-letter task (Rogers & Monsell, 1995) has also been used to assess switching (Montgomery *et al.,* 2005), with no clear ecstasy related deficit reported. Conversely Halpern *et al.* (2004) observed deficits in switching using the WCST. Interestingly, the cohort in this sample showed minimal exposure to any other drugs and as such potential confounds from polydrug use were reduced. However in a follow up study (Halpern *et al.,* 2011) with a larger sample and similar controls

for concomitant drug use and other lifestyle variables, no such behavioural deficits in relation to switching were observed. However Dafters *et al.* (2006) did observe deficits in ecstasy users over cannabis users and controls, in a task switching version of the Stroop task. As such the impact of MDMA exposure on this executive function remains unclear.

Despite equivocal behavioural results observed in previous research it would not be unreasonable to predict that ecstasy users may show reduced or altered set switching, as executive function is understood to rely heavily on areas of the prefrontal cortex. These frontal structures of the brain are rich in 5HT neurons (Pazos *et al.,* 1987), therefore potential serotonergic neurotoxicity or downregulation from regular use of MDMA may cause disruption to the cognitive processes that these areas maintain. Serotonergic neurotoxicity has been observed in various animal studies, however projecting these findings to humans is problematic (for a review see Easton & Marsden, 2006). Furthermore any executive function deficits observed with behavioural measures have been criticised due to potential confounds such as lack of sleep (Cole *et al*., 2002) and concomitant use of other drugs in ecstasy users. Many studies in this area attempt to control for this with the addition of a control group of drug users that have never taken ecstasy (Morgan, 1998**;** Reay *et al.,* 2006).

Progress has been made using EEG to observe central serotonin dysfunction in users. Burgess *et al.* (2011) observed ERP differences in late positivity over left parietal scalp sites associated with recollection between ecstasy users and controls, despite equivalent behavioural performance. The attenuation of this positivity in ecstasy users is evidence of a durable abnormality that would perhaps not have been identified by behavioural measures alone. There is evidence to suggest that ecstasy users may compensate behavioural differences with increased cortical activity compared to controls in fMRI studies (e.g. Daumann *et al.,* 2003). Typically cognitive impairment is associated with alterations to the P3 amplitude or latency due to the P3 being involved in higher level processing of stimuli.

This component encompasses frontal-parieto network activation (Gaspar *et al.* 2011) and in normal populations decreases in the amplitude potential reflects increased cognitive load, and diminished P3 reflects cognitive dysfunction. Longer latencies and smaller amplitude of the P3 response are indicative of cognitive impairment. Diminished P3 potentials have been observed in heavy and moderate ecstasy user groups in simple discrimination tasks (Casco *et al.* 2005) . Gamma *et al.* (2005) report observable reductions in the P3 amplitudes of ecstasy users in a Go/No-go task compared to controls, though this could be a polydrug effect. Conversely de Sola *et al*., (2008) report no significant differences between ecstasy users, cannabis users, and controls in P3 latency or amplitude in cognitive tests, though P3 latency was correlated with lifetime cannabis use. Ecstasy users also exhibit longer P3 latencies in detecting targets (Mejias *et al.* 2005). The P3 component is understood to be associated with the allocation of attentional resources necessary for information processing and also memory function (de Sola *et al*., 2008) and will consequently be implicated in switching. In normal populations larger P3 is observed in repeat trials compared to switch trials (Karayanidis et al., 2003) , indicative of a greater amount of available processing resources for non-switch trials, as opposed to switch trials (Goffaux, *et al.,* 2006) .

The aim of this investigation is to assess the cognitive processes supporting switching in ecstasy polydrug users compared to polydrug users who have not used ecstasy, and non-drug users. It is predicted that while behavioural deficits may not be apparent, differences in ERP components particularly in the P3 component will emerge, especially as this component is thought to play a role in higher level cognitive processing and is susceptible to degradation with cognitive decline. Specifically, it is predicted that ecstasy-polydrug users will have different electrophysiological responses during the task compared to polydrug users and nonusers consistent with cognitive impairment or reallocation.

2. Experimental Procedures

Design:

In all analyses the between groups factor was drug user group with 3 levels (ecstasy user, non-ecstasy polydrug user and drug naive controls). Univariate ANOVA was conducted on the behavioural data with the composite scores on the number-letter task (switch cost) as the dependent variable. ERP data was analysed using mixed ANOVA with electrode site as within participants, group between participants and amplitude as the DV for each ERP component.

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, 7 = male) and 20 non-ecstasy drug user controls (mean age=22.58, SD=0.79, 9 = male) were recruited[1] via direct approach to University students, whereby students were contacted via email or given information about the study during lectures and via the online research participation scheme (SONA systems). Participants were aged between 18-29 years and reported no neurological impairments. The ecstasy group must have taken ecstasy/MDMA on 5 or more occasions. The control group must have never used ecstasy/MDMA, however all other illicit substances were permitted for the non-ecstasy poly drug user 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 at the lab to confirm abstinence. Participants were also requested to abstain from use of other illicit drugs and alcohol for a minimum of 24 hours prior to participating and ideally 7 days. Tobacco smoking was permitted on the day of testing. All participants reported no current or last year diagnosis of psychological disorders.

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[1] Due to unusable data (from noise and artefacts), 18 ecstasy users, 20 polydrug users and 16 drug naive controls' EEG data was analysed.

Materials

Several questionnaires were issued to participants upon entering the lab. Participants completed a drug use questionnaire in which details of ecstasy use as well as other illicit drug use are requested. Using a method employed by Montgomery *et al.* (2005) 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.

State Mood

State Anxiety, Arousal and Hedonic Tone (Depression) were measured using scales devised by Fisk & Warr (1996). Participants are required to rate on a 5 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 subscale indicates increased hedonic tone/anxiety/arousal.

Ravens Progressive Matrices (Raven, Raven & Court, 1998)

Ravens standard progressive matrices (SPM) was used an indicator of fluid intelligence. This involves a series of problems (5 sets of 12, 60 in total), presented as a symbolic sequence. Participants are required to select an appropriate response to complete the sequence from a choice of 6 options. Successful completion of the task requires an understanding of the parts of the sequence and their interaction with one another. Each block of 12 problems begins with an intuitively simple problem and the problems become progressively more difficult as the task continues.

Mental set switching

This executive function was investigated using the number/letter task as per Rogers and Monsell (1995). During this task, number-letter pairs e.g. "B6" are displayed in one of 4 quadrants on a screen. If the number-letter pair appears in one of the top two quadrants, participants are to attend to the letter and respond to whether it is a vowel or a consonant. If in the bottom two quadrants participants are required to attend to the number and respond to whether it is odd or even. In the first block of trials the number/letter pairs alternate between the top two quadrants; in the 2nd block the pairs alternate between the bottom two quadrants. In the final block, the pairs are presented in anti-clockwise rotation, therefore every two responses requires a shift in the mental set between letters and numbers. The latency between the trials with the switch and those not requiring a switch is the "switch cost". The task is comprised of 6 blocks, the first two of which are practise blocks consisting to 62 trials in each. This is followed by 4 main blocks, each consisting of 64 trials (31 "switch" trials). There were 124 "switch" trials in total. There was an inter-trial interval of 1.5 seconds and participants were allocated an epoch of 5 seconds to respond. Participants were instructed to respond as quickly and as accurately as possible, and overall the task took around 20 minutes to complete.

Equipment

Electroencephalography (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), with electrodes 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). Vertical and horizontal electro-occulograms 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. Sigma electrolyte gel was used to ensure contact between scalp and electrodes. Data was digitized at a sampling rate of 512Hz 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 amounts of participants from each condition were tested in the morning as were in the afternoon. Upon entering the lab participants were given a brief description of the experiment and written consent was obtained. Following this participants were asked to give a urine sample, which was frozen at -25 Celsius until completion of data collection, when all samples were transported to University Hospitals Aintree for analysis. Participants were then asked 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, state mood scale and Raven's Progressive Matrices (Raven *et al*. 1998). Following completion of these questionnaires the EEG and actiview set up was tested and if necessary modified. The computerised task was then completed on a desktop computer running Inquisit version 3.0.6.0 (Millisecond software, 2011). Finally participants were fully debriefed and paid £20 in store vouchers. The study was approved by Liverpool John Moores University Research Ethics Committee, and administered in accordance with the ethical guidelines of the British Psychological Society.

EEG Analysis – Number-letter

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 0.1Hz and 40 Hz respectively. Any channels judged to be bad were replaced by interpolation and all data were EOG-corrected using BESAs 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 "switches", correct "non-switches" and incorrect "switches" and "non-switches") could be generated for each individual. Only ERPs for correct responses on the "switch" condition were included in the subsequent analysis. There were 124 "switch" trials in the entirety of the task. The mean number of good "switch" trials retained for grand averaging per subject was 96.37 (average 22.28% rejected trials), after rejecting incorrect trials (4.48%) and those containing artefacts (17.8%). Grand averages were made for each grouping condition (ecstasy user, polydrug user and drug naïve) on each task condition (correct "switches", correct "non-switches"). The overall P3 response was defined as the mean amplitude between 290 and 400 ms. (this time window was centred on the positive peak latency and the duration was chosen as this epoch contained the majority of positive activity for all conditions). Electrode activity was analysed in this epoch from occipitoparietal and occipital electrodes POz, PO3, PO4, PO7, PO8, Oz, O1 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 appeared to be largest over occipital and occipito-parietal sites P7, P8, POz, PO3, PO4, PO7, PO8, Oz, O1, and O2, between 170-220ms, this epoch was based around the mean local negative peak at these sites and encompassed the majority of negative activity over all 3 conditions. The P2 epoch was most visible as a positive peak between 200-250ms at frontal, frontocentral and central sites Fz, FCZ, FC1,

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FC2, FC3, FC4 and Cz. The mean amplitudes at these sites from the epoch based around the positive peak from the grand averages of all conditions were analysed.

<u>Urinary Analysis</u>

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 & Negative Ion Multiple Reaction Monitoring (MRM). Urine Specimens have been tested for the Synthetic Cannabinoids (JWH-018, JWH-073, JWH-250, JWH-398, JWH-122, JWH-019, AM-694, WIN 48098 & WIN-55212-2), as well as the 'designer' drugs 'Mephedrone', bk-MDMA or 'Methylone', bk-MBDB or 'Butylone', bk-PMMA or 'Methedrone', 1-benzylpiperazine, TFMPP, mCPP and MDPV. In addition they were tested for were a series of 12 Piperazine compounds, 4 β-Keto Amphetamines, a series of 11 Methcathinone compounds, 4-Fluoroamphetamine, Bupropion & the Hallucinogenic Amphetamines: D.O.B. ('bromo-STP' or 'Brolamphetamine'), D.O.C. and D.O.I. and 'Traditional' Drugs of Abuse: Amphetamine(s) including M.D.M.A., M.D.A. & M.D.E.A., Barbiturates, Benzodiazepines, THC & Cannabinoids, Buprenorphine, Cocaine & metabolites, Methadone & metabolites, Opiates & Opioids (Morphine, Codeine, Dihydrocodeine, Tramadol, d-Propoxyphene, Oxymorphone & Oxycodone), LSD, G.H.B. (and the Lactone Precursor), Psilocybin, Ketamine and Methaqualone.

<u>Statistical Analysis</u>

EEG data was analysed using a mixed ANOVA for each component (P2, N2, P3) with drug user group as the between subjects factor, electrode sites for the particular component as the within subject factor, and mean amplitudes at the various components at selected sites as the dependent variable. Any significant interactions or main effects between groups were further analysed using univariate ANOVA and Tukey HSD test.

State mood scores, fluid intelligence score and drug use variables are displayed in Table 1.

<<Insert Table 1 Here>>

One way ANOVA revealed that there were no significant between group differences on age, levels of arousal, depression and anxiety or total score on Ravens Progressive Matrices. 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 $t(17.88) = 2.02, p<.05$ (Levene's test was significant so degrees of freedom have been adjusted accordingly). Ecstasy users had also smoked significantly more joints within the last 30 days $t(16.01) = 1.86, p<.05$.

Urinary Analysis

Some drug metabolites were found in participants' urine. Specifically 3 ecstasy users' urine contained THC (mean 0.0083mg/l ± 0.01185), Δ-9-THC (0.16mg/l ± 0.18mg/l), 11-hydroxy-Δ-9THC (0.003mg/l ± 0.003). One ecstasy user's urine also contained 1-benzopiperazine (0.84mg/l) and TFMPP (0.18mg/l). One participant in the polydrug group had cannabis metabolites in their urine, specifically THC (0.001mg/l), Δ-9-THC (0.41mg/l) and 11-hydroxy-Δ-9THC (0.002mg/l)[2].

Behavioural Data Analysis

Incorrect answers were given a score of 0 and were not investigated any further. Mean reaction times were calculated for correct switch trials as well as correct non-switch trials so

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[2] Main analyses were re run excluding these participants. This did not change the direction or significance of results so analyses in the paper pertain to all participants.

that a switch cost could be calculated. Reaction time data reduction involved excluding

reaction times less than 200ms and greater than 4000ms. 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 1.27 (±0.73)

(rank = 24.58), polydrug users 1.64 (± 0.77) (rank = 33.75), drug naïve 6.56 (±22.0) (rank =

33.18), there were no between group differences in amount of outliers (H(2) = 3.53, $p > .05$).

Switch cost was calculated by subtracting the mean reaction time from 2 preliminary

blocks with no switching (all letters, followed by all numbers) from the mean reaction time

from the switch trials (from letters to numbers) in the main blocks of the task. One participant

in the drug naïve group had an incomplete dataset for this task and as such was excluded

from analysis. ANOVA revealed that there was no significant difference between groups on

switch cost $F(2, 56) = 0.41$, $p > .05$. Given the heavy use of cannabis in the ecstasy use group

in particular, and the possible confounding effects of sex, IQ and age on performance, a

stepwise regression analyses were conducted on the behavioural data, to observe whether

level use of ecstasy (after controlling for cannabis use, age, sex and IQ) was a predictor for

performance on the task. In step 1, age, sex and IQ (RPM total score) were entered as

predictors. This model accounted for a small and non-significant 3.6% of the variance in

switch cost (R^2change = 0.036, $F(3, 52) = 0.65$, $p > .05$) ($\beta = 0.01$; 0.05; 0.18 for sex, age and

IQ respectively, $p > .05$ in all cases). In Step 2, total lifetime dose of cannabis was entered as

a predictor, this model accounted for an additional non-significant 0.4% of the variance in

switch cost (R^2change = 0.004, $F(4, 51) = 0.53$, $p > .05$) ($\beta = 0.07$, $p > .05$). In the 3rd step,

total lifetime dose of ecstasy was entered as a predictor. This regression model accounted for

15.2% of the variance in switch cost. After controlling for age, sex, IQ and cannabis use, total

ecstasy use predicted an additional 11.2% of variance in switching deficits (R^2change = 0.11,

$F(5, 50) = 1.79$, $p > .05$). While the overall regression model was non-significant, total

lifetime dose of ecstasy emerged as the only significant predictor of switch cost after controlling for all of the other variables, meaning participants who had consumed a greater amount of ecstasy showed significantly poorer performance in this task ($\beta = 0.59$; $t(50) = 2.57$, $p<.01$). Furthermore, to investigate the effects of recent cannabis use, we performed the same regression analyses with amount smoked in the last 30 days replacing total lifetime dose as a predictor. In step 1, age, sex and IQ (RPM total score) were entered as predictors. This model accounted for a small and non-significant 3.6% of the variance in switch cost (R^2change = 0.036, $F(3, 52) = 0.65$, $p>.05$) ($\beta = 0.01$; 0.05; 0.18 for sex, age and IQ respectively, $p > .05$ in all cases). In Step 2, number of joints smoked in the last 30 days was entered as a predictor, this model accounted for an additional non-significant 0.5% of the variance in switch cost (R^2change = 0.005, $F(4, 51) = 0.54$, $p>.05$) ($\beta = 0.07$, $p >.05$). In the 3rd step, number of tablets used in the last 30 days was entered as a predictor. This regression model accounted for 8.9% of the variance in switch cost. After controlling for age, sex, IQ and cannabis use, total ecstasy use predicted an additional 4.8% of variance in switching deficits (R^2change = 0.048, $F(5, 50) = 0.98$, $p >.05$). There were no significant individual predictors.

ERP analysis

The grand averages for each group (users, polydrug non-users and drug naïve controls) can be observed at various electrodes measured for the separate components in Figures 2, 3 and 4. Mean amplitudes for each condition and electrode are given in Table 2. Due to some participants not completing the task and some unusable EEG data 6 participants are excluded from statistical analysis on the EEG data, 4 from the drug naïve group (n=16) and 2 from the ecstasy user group (n=18).

Mixed ANOVA[3] of mean amplitudes at component P3 (290-400ms) revealed a significant main effect of electrode site $F(4.04, 206.02) = 15.78$, $p<.001$, though the electrode x user group interaction was non-significant $F(5.05, 206.02) = 0.99$, $p>.05$. There was however a significant main effect of group $F(2,51) = 3.35$, $p<.05$. To further explore this difference, a series of one-way ANOVAs with group as between participants were conducted. This yielded significant effect of group at electrode O1 $F(2,51) = 3.80$, $p<.05$, with post hoc tests indicating that both drug using groups differed significantly from drug naïve participants ($p<.05$) but not from each other ($p>.05$). There were also significant differences at electrode POz $F(2,51) = 4.56$, $p<.05$, and again, post hoc analysis showed that both drug groups differed significantly from drug naïve participants ($p<.05$, one tailed) but not from each other ($p>.05$); There were also significant differences at PO4 $F(2,51) = 3.11$, $p<.05$, with post hoc tests indicating significant differences between polydrug and naive participants ($p<.05$).

Mixed ANOVA of mean amplitudes at component N2 (170-220) revealed a significant main effect of electrode $F(4.27, 217.82) = 12.23$, $p<.001$. The electrode x user group interaction $F(8.54) = 217.81) = 0.76$, $p>.05$, and the main effect of group $F(2,51) = 1.83$, $p>.05$, were however non-significant so this component is not discussed further.

At component P2 (200-250ms) Mixed ANOVA revealed a non-significant effect of electrode $F(3.30, 168.44) = 1.60$, $p>.05$, though the electrode x user group interaction was significant $F(6.61, 168.44) = 2.12$, $p<.05$. The main effect of group was not significant for this component $F(2,51) = 2.11$, $p>.05$. To further explore the nature of the significant interaction, a series of one way ANOVAs were used. These yielded significant group differences at

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[3] In all mixed ANOVAs, Mauchley's test was significant so adjusted degrees of freedom are reported in line with the Greenhouse Geisser statistic.

electrode Fz $F(2,51) = 3.52$, $p<.05$, with post hoc analysis showing that ecstasy polydrug users differed from both other groups ($p<.05$); at electrode FCz $F(2,51) = 5.66$, $p<.01$, with ecstasy polydrug users differing from both other groups ($p<.05$); and at electrode Cz $F(2,51) = 3.14$, $p<.05$, with ecstasy polydrug users differing from both other groups ($p<.05$ one tailed). Inspection of Table 2 suggests that for all the electrodes, ecstasy users have higher mean P2 amplitudes than the other two groups, with the exception of electrode FC3, where the opposite pattern is seen.

4. Discussion

The aim of this study was to examine the processes involved in mental set switching in ecstasy users, using a number-letter task. The control groups did not differ from the ecstasy users on the background variables such as fluid intelligence, age and state mood. Nor did they differ on the number-letter task in terms of number of switch cost or errors. A regression analysis revealed that after controlling for cannabis use, level use of ecstasy predicted performance deficits behaviourally. This is in line with previous research on amphetamine users (Ornstein, 2000) which suggests that more chronic use leads to a greater deficit in mental set switching, as well as Halpern *et al.* (2004)'s original study who observed greater performance deficits on this task in heavy ecstasy users than light users.

The electrophysiological data also provide support for deficits in this executive function with drug use. The P3 component, thought to play an important role in the allocation of attentional resources and as such an important role in the ability to switch between mental sets, showed significant between group differences at several occipito-parietal and occipital electrode sites. Nonusers displayed a significantly higher mean amplitude in this component (290-400ms) compared to ecstasy users as well as polydrug controls. A diminished P3 component is thought to reflect cognitive impairment, and as such these findings are in line with those of Casco *et al.* (2005) and Mejias *et al.* (2005) who have observed reduced P3 in ecstasy users compared to controls in other cognitive tasks. Interestingly, the polydrug control group appear to have a reduced P3 in several areas compared to drug naive controls, suggesting some evidence of atypical processing that is related to the use of drugs in general and not just ecstasy i.e. a polydrug effect. Furthermore, it has been suggested previously that concomitant cannabis use may account in part or fully for cognitive deficits observed in ecstasy users (Dafters et al., 2004; Gamma *et al.,* 2005), though in the present study, level of ecstasy use appears to be a more important predictor.

Analysis of the N2 component provided some interesting findings, with ecstasy users and polydrug users generally showing greater negativity compared to drug naïve controls at the electrodes measured (occipito-parietal and occipital sites). These differences were only significant between ecstasy users and drug naïve controls at site P7, and differences between these groups were approaching significance at two more sites (PO7 and O1). There were, however, no observable differences between ecstasy users and polydrug controls in this component. This component is thought to reflect conflict monitoring and is also reported to be greater in trials with high conflict (Yeung & Cohen, 2006). Perhaps higher mean amplitude in this component would reflect inefficiency in processing this type of information.

Differences were also apparent in the P2 component, involved in early processing of stimuli. It was observed that ecstasy users displayed a significantly higher mean amplitude than both control groups at fronto-central site FCz. Further to this, the ecstasy users were approaching significance for higher mean amplitude than polydrug controls at central site CZ and approached significance for having a higher mean amplitude compared to both groups at frontal midline site Fz. Atypicalities at this early stage of processing in ecstasy users appear to provide evidence to suggest additional resources are being recruited as a compensatory mechanism. Perhaps additional recruitment of resources at this stage allowed for similar results behaviourally, despite a diminished P3 amplitude at a later stage of processing.

These results suggest evidence for an ecstasy/polydrug effect on the degradation of the executive function of mental set switching. Few previous studies have found cognitive atypicalities (Halpern *et al.,* 2004), however those who have previously suggested no deficit in this executive function have neither had the purity of the cohort examined in the Halpern *et al.,* (2004) study, nor perhaps equivalent lifetime dose. However in the follow up study (Halpern *et al.,* 2011) using participants with minimal exposure to other drugs and a larger

sample size, the effects of MDMA on switching were not evident, so perhaps of greater

importance, is the use of more sensitive measures of cognitive impairment such as EEG.

Limitations:

Unlike the relatively "pure" MDMA user groups in the two studies by Halpen *et al.*

(2004 & 2011)**,** the current ecstasy user group tended to take several other drugs – in

particular cannabis. Although we attempted to control for this with the addition of a polydrug

control group, it was apparent that the ecstasy user group smoked significantly more cannabis

and consumed significantly more cocaine than this group. Furthermore there were 9

participants in the ecstasy user group who reported using ketamine in the last 30 days,

compared to none in the polydrug group, this is potentially problematic for the interpretation

of the current results given the association between ketamine use and executive function

deficits in humans (for a review see Morgan & Curran, 2006), and specifically that switching

has been shown to be impaired in animals with ketamine exposure (Stoet & Snyder, 2006).

Moreover, the polydrug user group also showed a diminished P3 response compared to drug

naive controls in several sites, so perhaps it would be more accurate to call the observed

effects "polydrug effects". With this in mind, it can also not be ruled out that premorbid

factors do not predict drug use, and that such factors (for example differences in sensation

seeking) contribute to the observed differences in the present study. In addition, the self

reporting of psychological state is potentially problematic and in future research, a structured

psychiatric assessment may be more appropriate. Tobacco use was also not controlled for in

the current study, there has been previous research to suggest that tobacco smoking has an

affect on EEG measures (Illan & Polich, 2001**;** Gilbert et al., 2004). In particular abstinence

from tobacco smoking in normal users of tobacco, has shown performance and activity

decline that can last for up to 31 days (Gilbert et al., 2004). However, smokers were

permitted to smoke tobacco on the day of testing so this is unlikely to have affected the

results reported here. The quasi-experimental design employed here also means that the current authors cannot state that the individual differences witnessed here are not the result of factors other than drug use, though we have attempted to control for many of these such as fluid intelligence, age, state mood and residual intoxication of drugs. Residual intoxication of alcohol was self-report, but in future studies it would be advantageous to verify this with a breathalyser to ensure no residual alcohol intoxication. Self report measures for background drug use are also problematic, however because of the legal status of the drugs consumed, this remains the most appropriate measure of background drug use, and is also the most commonly used in this area of research (Fox *et al.,* 2001; Montgomery *et al.,* 2005; Montgomery *et al.,* 2010). The purity of the tablets consumed by the current set of participants as well as the strength of the cannabis being consumed is questionable. However, Parrott (2004) reported that the purity of ecstasy tablets collected from amnesty bins in nightclubs in the UK is approaching 100%. However if this is not the case then this raises additional concerns over the magnitude of cognitive deficits incurred (Montgomery *et al.,* 2010).

The present study provides evidence for differences in cognitive function in ecstasy/polydrug users. Given its association with resource allocation and higher level processing, electrophysiological differences in the P3 component suggest a deficit in the cognitive resources necessary for normal functioning in the set switching task. Furthermore atypical early processing of stimuli in ecstasy users is suggestive of compensatory mechanisms used to attenuate behavioural differences due to disturbances in normal processing. Moreover after controlling for cannabis-related effects, regression analysis suggests that set switching performance declines with increased use of ecstasy. The broader implications here suggest reduced cognitive flexibility with increased drug use. The inability to rapidly adjust behaviour to suit environmental changes has consequences for real world

situations, for example the ability to which ones job can be performed adequately. Furthermore, as this sample was relatively young, it would be interesting to observe persistent problems with cognitive flexibility in an ageing population with a history of heavy drug use.

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Table 1: Background Variables

	Ecstasy Users			Non-Ecstasy Drug Users			Drug Naïve Controls		
	Mean	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
RPM (max= 60)	48.68	5.96		48.35	5.83		51.35	5.01	
State anxiety	11.4	4.08		12.44	2.18		11.75	2.12	
State depression	13.1	3.91		12.61	2.4		12.1	3.14	
State arousal	19.7	4.54		20.5	3.68		20.1	3.02	
Ecstasy									
Frequency (times/wk)	0.24	0.42	12	-	-	-	-	-	-
Last 30 days (Tablets)	0.60	2.26	20	-	-	-	-	-	-
Total use (Tablets)	177.65	301.73	20	-	-	-	-	-	-
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 p/w	15.33	15.29	20	10.53	8.37	20	9.93	11.58	20
Tobacco cigarettes p/d	6.98	6.32	13	7.1	5.48	5	1		1

RPM = Raven's Progressive Matrices; * significant difference at p<.05

Table 2: Mean amplitudes across components, for each electrode measured.

	P3									
	PO7	*PO3*	*O1*	*Oz*	*POz*	*PO8*	*PO4*	*O2*		
Ecstasy	1.25 (2.13)	2.59 (1.63)	0.68 (1.84)	0.40 (1.52)	2.67 (2.37)	1.63 (2.58)	2.24 (1.70)	0.37 (1.76)		
Polydrug	1.94 (2.05)	2.57 (1.54)	0.71 (1.90)	0.27 (1.72)	2.27 (0.94)	0.92 (3.11)	1.94 (1.77)	0.32 (2.82)		
Drug Naive	2.03 (2.20)	3.56 (2.61)	2.37 (2.41)*	1.66 (2.33)	4.50 (3.26)	1.56 (3.49)	3.61 (2.75)	1.93 (2.72)		

	N2								*P7*	*P8*
Ecstasy	-2.56 (0.61)	-0.90 (0.46)	-1.58 (0.53)	-0.15 (0.48)	0.45 (0.60)	-0.66 (0.78)	-0.06 (0.60)	-0.48 (0.60)	-2.81 (0.46)*	-1.36 (0.63)
Polydrug	-2.08 (0.57)	-0.70 (0.44)	-1.17 (0.50)	0.47 (0.45)	0.81 (0.57)	-1.44 (0.74)	0.12 (0.57)	0.39 (0.57)	-1.88 (0.44)	-0.87 (0.60)
Drug Naive	-0.60 (0.64)	0.05 (0.50)	0.20 (0.56)	0.70 (0.51)	1.09 (0.64)	-0.45 (0.82)	0.57 (0.64)	0.56 (0.63)	-0.66 (0.49)*	-0.13 (0.67)

	P2									
	FC3	*FC1*	*Fz*	*FC4*	*FC2*	*FCz*	*Cz*			
Ecstasy	-0.18 (4.22)	1.07 (1.38)	1.54 (1.63)	1.66 (1.33)	1.57 (1.24)	2.10 (1.45)	1.78 (1.24)			
Polydrug	0.95 (1.18)	0.65 (1.34)	0.37 (1.84)	1.61 (1.64)	1.10 (1.69)	0.64 (1.43)	0.45 (2.34)			
Drug Naive	0.96 (2.30)	0.74 (1.86)	0.28 (1.12)	0.88 (1.53)	0.59 (1.29)	0.59 (1.71)	0.47 (1.63)			

Figure 1. Grand Average Waveforms for the 3 Groups Across Electrodes: O1, Oz, POz and PO4 (correct switches)
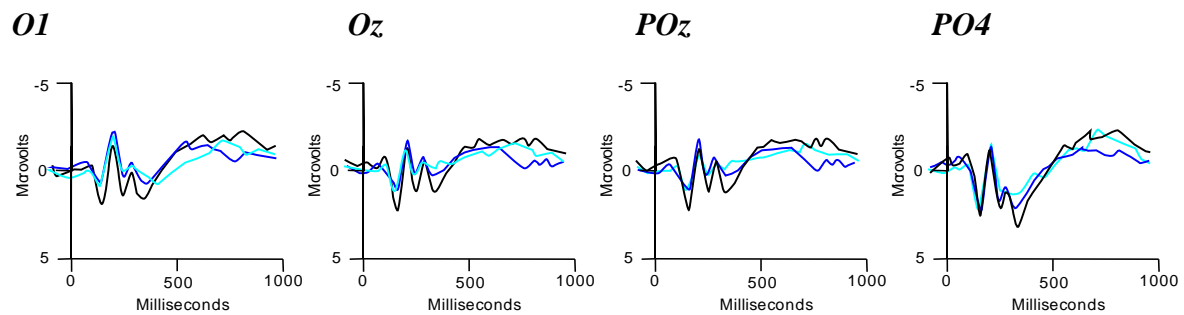

Fig. 1: Depicts the waveforms from electrodes that showed significant group differences in the P3 component. Ecstasy users are displayed in (blue), polydrug users are displayed in (black) and drug naïve controls are displayed in (lilac). These waveforms are from grand averaged data from each user group. The significant differences between ecstasy users and drug naïve controls as well as polydrug users and drug naïve controls can be seen in O1, the difference (approaching sig) between polydrug users and naives can be seen in Oz (between 290-400ms). The significant differences between these groups in this component can be viewed again in POz, this time the difference between ecstasy users and drug naïve controls is approaching significance and finally PO4 depicts the difference between polydrug users and drug naïve controls

Figure 2. Grand Average Waveforms for the 3 Groups Across Electrodes: P7 and PO7 (correct switches)
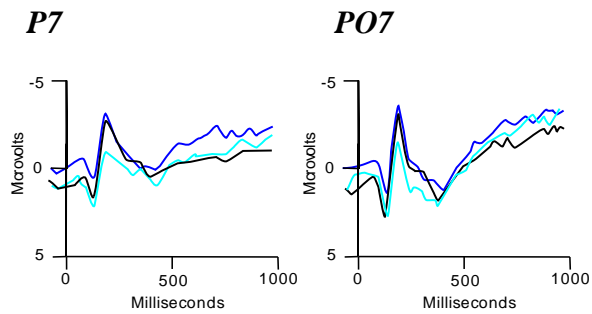

Fig. 2: Depicts the waveforms from electrodes that showed significant group differences in the N2 component. Ecstasy users are displayed in (blue), polydrug users are displayed in (black) and drug naïve controls are displayed in (lilac). P7 shows the significant difference between ecstasy users and drug naïve controls, this difference is approaching significance and can be observed in PO7, to observe the difference that is approaching significance in O1 see Figure 1.

Figure 3. Grand Average Waveforms for the 3 Groups Across Electrodes: Fz, FCz and Cz (correct switches)
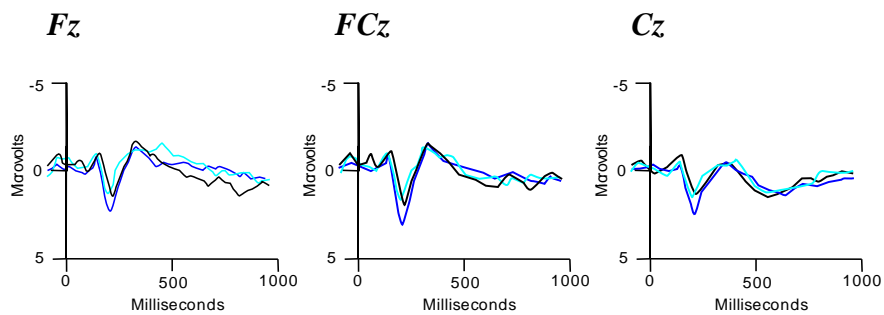

Fz *FCz* *Cz*

Fig. 3: Depicts the waveforms from electrodes that showed significant group differences in the P2 component. Ecstasy users are displayed in (blue), polydrug users are displayed in (black) and drug naïve controls are displayed in (lilac). The significant differences between ecstasy users and both control groups can be seen in FCz (200-250ms), the difference (approaching sig) between ecstasy users and the two control groups can be seen in Fz. Finally in Cz the difference between ecstasy users and polydrug users (approaching sig) can be observed.