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Abstract

Background: Cognitive deficits are well documented in ecstasy (MDMA) users with such deficits being taken as evidence of dysregulation of the 5HT system. More recently neuroimaging has been used to corroborate these deficits. The present study aimed to assess multitasking performance in ecstasy polydrug users, polydrug users and drug naïve individuals. It was predicted that ecstasy polydrug users would perform worse than nonusers on the behavioural measure and this would be supported by difference in cortical blood oxygenation. *Methods:* Twenty ecstasy-polydrug users, 17 polydrug users and 19 drug naïve individuals took part. On day 1 drug use history was taken and questionnaire measures were completed. On day 2, participants completed a 20 minute multitasking stressor while brain blood oxygenation was measured using functional near infrared spectroscopy (fNIRS). *Results:* There were no significant differences between the 3 groups on the subscales of the multitasking stressor. In addition, there were no significant differences on self-report measures of perceived workload (NASA – TLX). In terms of mood, ecstasy users were significantly less calm and less relaxed compared to drug-naïve controls. There were also significant differences at 3 voxels on the fNIRS indicating decreased blood oxygenation in ecstasy users compared to drug naïve controls at V2 (left DLPFC), V14 and V16 (right DLPFC), and compared to polydrug controls at V14. *Conclusions:* The results of the present study provide support for changes in brain activation during performance of demanding tasks in ecstasy polydrug users, which could be related to cerebral vasoconstriction.

1. Introduction

Recreational drug use is argued to be detrimental to normal physiological and psychological functioning. Various studies have found cognitive deficits in ecstasy/MDMA users (Montgomery *et al.*, 2010; Parrott & Lasky, 1998; Wareing *et al.*, 2004). While some studies have shown deficits in executive functioning (Fisk *et al.*, 2004; Montgomery *et al.*, 2005), a number of recent reviews have shown the most prominent and persistent deficits are in learning and memory, particularly verbal recall (Gouzoulis-Mayfrank & Daumann, 2009; Kalechstein et al., 2007; Zakzanis et al., 2007). The acute psychological and physiological effects are thought to result primarily from serotonin and dopamine agonsim (McDowell & Kleber, 1994), with repeated exposure purported to damage serotonin neurons resulting in problems with cognition, sleep and mood (Parrott *et al.*, 2000; Parrott, 2013). In animal studies MDMA administration mirroring human recreational doses has a deleterious effect on serotonergic neurons (Green *et al.*, 1995). Such serotonergic neurotoxicity is a possibility in humans, especially with higher nightly doses (McCann *et al.*, 1994). Moreover the neuronal areas implicated in working memory and executive functioning are often observed to be localised in the dorsolateral pre-frontal cortex (Curtis & D'Esposito, 2003). These structures are densely innervated with 5-HT receptors (Pazos *et al.*, 1987), thus serotonergic neurotoxicity or down-regulation may result in cognitive deficits specific to functions that these areas maintain (Montgomery & Fisk, 2008; Reneman *et al.*, 2006).

Neuroimaging techniques (EEG, fMRI, fNIRS) are increasingly used in drug research to provide neurophysiological correlates of behavioural deficits, or indeed perhaps as a more sensitive measure of cognitive impairment. For example Burgess *et al*. (2011) assessed ecstasy users' performance on verbal and non-verbal recognition memory, with ERP measures compared to two control groups (drug naive participants and polydrug users who do not use ecstasy). Ecstasy users displayed abnormalities in an ERP component associated with

recollection of words but not faces, despite equivalent behavioural performance. Similarly Kanayama *et al*. (2004) observed fMRI differences in cannabis users compared to controls during a spatial working memory task despite the absence of behavioural differences. Bosch et al. (2013) have also shown a direct link between brain glucose metabolism in the dorsolateral prefrontal cortex (DLPFC) and level of MDMA use. MDMA users were impaired relative to controls on the Rey Auditory Verbal Learning Test (RAVLT) and showed significantly decreased glucose metabolism in various brain areas including the right hippocampus, bilateral DLFPC, bilateral thalamus and inferior parietal cortex. In the MDMA users, positive correlations were observed between glucose metabolism in the prefrontal and parietal areas and RAVLT performance. Importantly, lifetime MDMA dose was significantly negatively related to glucose metabolism in the left DLPFC. These studies highlight the importance of investigating brain indices of cognitive performance in addition to behavioural indices.

The present study employed Functional Near-Infrared Spectroscopy (fNIRS). fNIRS is a novel, non-invasive, optical neuroimaging technique that is portable and is used to measure the haemodynamic response to brain activation (Leff *et al*., 2011). Typically fNIRS will penetrate to structures around 2-3 mm of the cortex underlying the skull (Firbank *et al*., 1998). Therefore forebrain structures such as the DLPFC can be easily accessed and observed. Activation of the DLPFC is prominent in higher level processing, and due to these structures being easy to access with this type of imaging, it has been used in several studies observing motor control and learning (Leff *et al*., 2011), as well as more complex tasks that involve working memory and category discrimination (Izzetoglu, 2004). Generally an increase in the chromophore Hbo2 (oxyhaemoglogin) coupled with a decrease in Hhb (deoxyhaemoglobin) is accepted as being reflective of activation to a certain brain region (Ehlis *et al*., 2008; Leff *et al.,* 2008 Leff *et al.,* 2011) and the distribution of this response is regionally specific; thus

the cortical regions underlying certain optodes of the fNIRS headset are understood to be responsible for the observed response (Leff *et al.,* 2011).

Although currently there remains a paucity of studies conducted with fNIRS and substance use (specifically ecstasy/MDMA use), it has been used in other populations with working memory problems. Ehlis *et al*. (2008) observed a significant reduction in Hbo2 over ventrolateral prefrontal cortex channels in ADHD patients compared to controls in relation to a working memory *N*-back task. It was argued this reflects a reduction in activation of this area of the brain during task performance. Interestingly this was not accompanied by significant behavioural differences (although a trend was observed). Similarly Schecklmann *et al.* (2008) report lower concentration of Hbo2 in ADHD patients relative to controls during two versions of a verbal fluency task, suggesting that executive functioning deficits are associated with decreased oxygenation to the brain areas that underlie performance of these tasks.

The present study aims to investigate changes in prefrontal blood oxygenation in response to a demanding task in ecstasy users, polydrug users and nonusers. The cerebral hemodynamic response to conducting several tasks at once will be measured as well as behavioural performance. It is hypothesised that ecstasy users will perform worse on the multi-tasking stressor and fNIRS will provide corollary data of this by displaying a reduction in oxygenated haemoglobin in comparison to the control groups.

2. Method:

2.1 Design:

For behavioural and fNIRS analysis a between groups design was used, with a between groups factor of drug user group with 3 levels (ecstasy user, polydrug user and drug naïve

controls. Univariate ANOVA was conducted on the behavioural data with the total scores on each component of the task as the dependent variables (Stroop, mental arithmetic, tracking/target area – visual monitoring and warning/rising bars – visual monitoring)**.** fNIRS data was analysed using univariate ANOVA with mean oxygenated haemoglobin at each voxel measured as the dependent variables (voxels 1-16). Any significant main effects were further investigated using Tukey's HSD.

2.2 Participants:

Twenty ecstasy users (mean age: 21.61±0.52; 12 male), 17 non-ecstasy-polydrug user controls (mean age: 21.23±0.79; 12 male) and 19 drug naïve controls (mean age: 21.60±0.84; 6 male) were recruited via direct approach to Liverpool John Moores University students. For inclusion in the study participants had to be aged between 18 – 29 years. For inclusion in the ecstasy/MDMA user group, participants must have used ecstasy/MDMA on at least 5 occasions over their lifetime (actual minimum = 7 tablets) but may have used a range of substances in addition to MDMA. To be included in the non-ecstasy polydrug user group, participants must have consumed illicit drugs on at least 3 occasions in the last 12 months, but never have consumed ecstasy/MDMA, and finally for inclusion in the drug naïve control group participants must have never consumed any illicit drugs. All participants were asked to abstain from consuming ecstasy for a minimum of 7 days prior to testing. Participants were also requested to abstain from use of other illicit drugs for a minimum of 24 hours prior to participating and ideally 7 days.

2.3 Materials

A background drug use questionnaire (Montgomery *et al.,* 2005) was administered. Estimates of total lifetime drug use of each drug were calculated (as per Montgomery *et al.,* 2005) as well as totals for last 30 days drug use and weekly drug use estimates.

The *SAI VAS (State Anxiety Inventory – Visual Analogue Scale)* was completed pre and post testing period, this comprises 6 statements (I feel calm, I feel tense, I feel upset, I feel relaxed, I feel content, I feel worried) and participants have to indicate on a 100mm line how much they agree with the statement, ranging from 0 – not at all, to 100 – very much.

Multitasking stress test

The multi-tasking framework (Purple Research Solutions, UK) is a PC ran platform used to elicit acute psychological stress (Wetherell & Sidgreaves, 2005). The same combination of four stressor modules (Stroop, mental arithmetic, tracking/target area – visual monitoring and warning/rising bars – visual monitoring) was used for all participants, at a medium intensity workload. The task requires participants to attend to the 4 different components/modules of the task simultaneously. The set of tasks include a mental arithmetic task whereby participants are required to calculate a series of 2 x 3 digit addition sums; visual monitoring (target area) whereby participants must monitor the position of a moving cursor and reset this cursor when it enters a points zone; a second visual monitoring module (rising bars) comprises of a set of 6 bars that rise towards a target line at varying speeds. Once the bars have reached the target, participants must select the order of which the bars reached the target, fastest first; and finally a Stroop task module involves colour names appearing onscreen in various colours, participants must correctly select the colour the word appears in, rather than the written word. For more information on the different modules of the framework, see Wetherell and Sidgreaves (2005).

Equipment

Haemodynamic response to task was monitored using a continuous wave fNIRS system developed by Drexel University (Philadelphia, PA) and supplied by Biopac systems (Goleta, CA, USA). The fNIR sensor has a temporal resolution of 500ms per scan (2Hz), with a

source-detector separation of 2.5cm allowing 1.25cm penetration depth (Ayaz *et al.,* 2012). An fNIR100 control box and data acquisition and visualisation software COBI studio (Drexel university) were used during data collection (as per Ayaz *et al.,* 2011; Ayaz *et al*., 2012) with a serial cable between display and acquisition PCs to identify task markers.

2.4 Procedure

Participants were required to attend the lab on 2 occasions. On Time 1, upon entering the lab participants were informed of what the study would entail and written consent was obtained. Participants were given the background drug use questionnaire and an assessment of fluid intelligence (Raven's Progressive Matrices- RPM Raven *et al.,* 1998) to complete. On Time 2, a pre-task SAI-VAS was given upon entering the lab. After this the fNIRS sensor pad was attached to the participants' forehead whilst they read instructions on how to complete the task. Participants then completed an easy two minute practise trial of the task. The fNIRS signals were displayed on a desktop computer running COBI studio (Drexel University) in an adjacent room to the testing room. Providing the signals from the fNIRS were stable, a baseline of inactivity was recorded before the participants were instructed to complete a 20 minute session of the multi-tasking stressor task on a desktop computer running the purple framework (Purple Solutions, UK). After the 20 minutes had elapsed, participants completed a post task SAI-VAS. The NASA TLX (Task Load Index - Hart *et al.,* 1988) was completed post task to measure perceived workload. Finally, participants were 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.

2.5 fNIRS Analysis

fNIRS raw data from COBI studio was pre-processed using fnirSoft (Ayaz, 2010). All 16 optodes (oxy and deoxy haemoglobin) were visually inspected for any saturated channels, and any saturated channels were discarded. A high-pass filter (0.1Hz cut off) and a linear phase filter (order of 20) were used to remove high frequency noise and noise due to respiration (Ayaz *et al.*, 2011; Ayaz *et al*., 2012). Using the modified Beer-Lambert law logarithm in fnirSoft (Ayaz, 2010), we calculated total blood oxygenation, deoxygenation and volume changes relative to baseline over the entire epoch for the 16 channels.

3. Results

RPM scores and pre and post task SAI-VAS scores are displayed in Table 1. Indices of other drug and alcohol use are displayed in Table 2.

<<Insert Tables 1 & 2 Here>>

One way ANOVA revealed that there were no significant between group differences on age and fluid intelligence (p>.05 in both cases). Pre and post task SAI-VAS scores for each of the six subscales (calm, tense, relaxed, content, upset and worried) were analysed using a mixed ANOVA, with user group as the between subject factor and timepoint (pre/post) as the within subjects factor. For *calm* there was no significant main effect of time point $F(1, 53)=0.19$, p>.05 and no time point by group interaction $F(2, 53)=1.97$, p>.05, but there was a main effect of group $F(2, 53)=3.08$, $p\leq.05$. Pairwise comparisons showed that ecstasy users felt less calm than both other groups (p<.05). For *tense* there was a significant main effect of time point $F(1, 53)=3.95$, $p \leq .05$, with ecstasy and polydrug users showing increases at Time 2, but no timepoint by group interaction $F(2, 53)=0.32$, p>.05, and no main effect of group $F(2, 53)=1.75$, p>.05. *Upset* showed no main effect of timepoint $F(1, 53)=1.69$, $p > .05$, no timepoint by group intereaction $F(2, 53)=1.82$, $p > .05$ and no main effect of group $F(2, 53)=0.07$, $p > .05$. *Relaxed* also showed no main effect of time point $F(1, 53)=0.03$, $p > .05$

and no timepoint by group interaction $F(2, 53)=0.05$, $p > .05$, but does show a significant main effect of group $F(2, 53)=3.04$, $p \leq .05$. Pairwise comparisons revealed that drug naïve controls were significantly more relaxed than ecstasy users ($p<.05$). *Content* revealed no significant effect of timepoint $F(1, 53)=0.25$, $p > .05$, no timepoint by group interaction $F(2, 53)=0.33$, $p > .05$, and no main effect of group $F(2, 53)=1.39$, $p > .05$. Finally, *worried* revealed a main effect of timepoint $F(2, 53)=3.04$, $p \leq .05$, with worry being greatest pre task, but no timepoint by group interaction $F(2, 53)=0.27$, $p > .05$, and no main effect of group $F(2, 53)=1.06$, $p > .05$.

ANOVA revealed a between group difference in the amount of alcohol consumed (weekly) $F(2, 52)=3.28$, $p<.05$. Pairwise comparisons revealed that the ecstasy users drank significantly more than drug naive controls $p \leq .05$.

3.1 Behavioural Data Analysis

The multi-tasking stressor task was developed by purple solutions (Purple research solutions, UK) and performance was analysed using SPSS (17). Due to 8 participants (4 ecstasy users, 3 polydrug users and 1 drug naïve control) not following instructions correctly on the Stroop task and consistently answering incorrectly on the task, their data on this component on the task was not analysed any further. These participants are also excluded from fNIRS analysis. Performance data can be observed in Table 3

<<Insert Table 3 About Here>>

There were no significant differences between groups on any of the components of the task; Stroop $F(2,45)=0.08$, $p>.05$; Maths $F(2,53)=0.56$, $p>.05$; Tracking/target visual monitoring $F(2,53)=0.50$, $p>.05$. Levene's statistic was violated on the warning/rising bars scores, therefore an independent samples Kruskall-Wallace test was conducted. This revealed that there were no significant differences between ecstasy users (rank = 560), polydrug

controls (rank = 570) and drug naïve controls (rank = 580) on this component of the task; (H(2) =1.43, p>.05). On the composite total score, ANOVA revealed no significant between group differences F(2,45)=0.55, p>.05.

Post task NASA TLX scores were analysed using MANOVA. This revealed no overall between group differences in task load F(12,96)=1.25, p>.05 for Pillai's trace, nor any between group differences on the individual sub-scales (Mental demand; F(2,52)=1.32, p>.05, Physical demand; F(2,52)=0.11, p>.05, Temporal demand; F(2,52)=0.10, p>.05, Effort; F(2,52)=1.97, p>.05, Performance; F(2,52)=2.39, p>.05, Frustration; F(2,52)=2.65, p>.05).

3.2 fNIRS Analysis

Averaged oxygenated and deoxygenated haemoglobin changes from baseline are displayed Figures 1 and 2. A series of ANOVAs[1] were used to assess group differences in changes from baseline. This analysis was conducted due to large concentration increases in oxygenated haemoglobin and decreases in deoxygenated haemoglobin being understood to represent increased levels of neurological activation (Hoshi *et al.*, 2001; Cui *et al.*, 2010; Ayaz *et al.*, 2011;) and also due to each voxel theoretically relating to a different brain region.

<<Insert Figures 1 & 2 About Here>>

ANOVA revealed significant between group differences in average oxy-Hb changes at voxel 2 F(2,43)=4.78, p<.05; V14 F(2,43)=6.37, p<.01 and V16 F(2,42)=3.32, p<.05. There were no significant between group differences at any of the other voxels measures (p>.05).

[1] Due to small amounts of missing data on different optodes, MANOVA was not appropriate for this analysis.

Pairwise comparisons revealed that at V2 ecstasy users showed a significantly reduced oxy-Hb change compared to drug naïve controls ($p<.05$). At V14 ecstasy users show significantly lower oxy-Hb than both polydrug controls ($p<.01$) and drug naïve controls ($p<.05$). At V16 ecstasy users again show significantly lower oxy-Hb than drug naïve controls ($p<.05$).

ANOVA on deoxy-Hb changes from baseline revealed significant between group differences at V1 $F(2,42)=3.96$, $p<.05$, V2 $F(2,43)=4.71$, $p<.05$, V4 $F(2,30)=3.66$, $p<.05$, V12 $F(2,30)=5.04$, $p<.05$ and V14, $F(2,43)=5.09$, $p<.01$. There were no significant between group differences at any of the other voxels measured ($p>.05$).

Pairwise comparisons revealed that at V1, polydrug controls showed significantly greater deoxy-Hb than drug naïve controls ($p<.05$), and this difference approached significance compared to ecstasy users ($p=.07$). At V2, polydrug controls showed significantly greater deoxy-Hb increase than ecstasy users ($p<.05$) and this difference approached significance compared to drug naïve controls ($p=.08$). At V4 polydrug controls showed significantly increased deoxy-Hb compared to drug naïve controls ($p<.05$). At V12 polydrug controls showed significantly increased deoxy-Hb compared to both ecstasy users and drug naïve controls ($p<.05$ in both cases) and at V14 polydrug controls showed significantly greater deoxy-Hb compared to ecstasy users ($p<.01$). Ecstasy users and drug naïve controls did not differ significantly from each other at any of these voxels.

These results show a general blunted increase in oxygenated haemoglobin during the tasks for ecstasy users relative to drug naive controls at voxels 2, 14 and 16. Ecstasy users also displayed significantly reduced oxy-Hb change at V14 compared to polydrug controls. Furthermore, as to be expected due to a general inverse correlation between oxygenated and deoxygenated haemoglobin usually observed in neurological activity, ecstasy users have

shown a significantly reduced decrease in deoxygenated haemoglobin compared to drug naïve controls at V1, and relative to polydrug controls at V2, V12 and V14.

Relationship between cortical blood changes and drug use.

To assess the relationship between the changes in cortical blood flow observed using fNIRs and parameters of drug use, we used Spearman's correlations. Results are displayed in Table 4; all correlations are evaluate at $p<.01$ to adjust for multiple comparisons.

<<Insert Table 4 About Here>>

There were a number of significant correlations between ecstasy use and oxygenation change. Notably, frequency of use was significantly correlated with V2 (left inferior DLPFC), 6 & 8 (left inferior mid PFC) and 14 (right inferior DLPFC), total lifetime dose with V2 (left inferior DLPFC), 6 & 8 (left inferior mid PFC) and 14 & 16 (right inferior DLPFC), while amount used in the last 30 days was significantly correlated with V2 & 4 (left inferior DLPFC), 8 (left inferior mid PFC) and 14 & 16 (right inferior DLPFC). There were 2 significant correlations with indices of drug use, with frequency of cannabis use correlated with V8 and frequency of cocaine use with V14. In both cases the correlations were weaker than those for ecstasy. For deoxygenation change, total lifetime dose of ecstasy was significantly correlated with V14 (right inferior DLPFC).

4. Discussion

The aim of the current study was to investigate the effects of ecstasy use on a multitasking stress test and to assess drug related differences in haemodynamic response to task. The ecstasy users in this study did not differ significantly from controls on background variables such as perceived stress, fluid intelligence or age. Nor did they differ significantly

on any of the individual components that made up the multi-tasking stressor task, or on perceived workload as measured by the NASA TLX. There were however differences on subscales of the SAI VAS, indicating that ecstasy users felt less calm than both other groups overall and less relaxed than drug naïve controls. Furthermore, as to be expected, all groups were less worried post task.

Despite an absence of between group differences on behavioural measures, the fNIRS data revealed several significant differences that are worthy of discussion. Ecstasy users displayed a significant reduction in oxygenated haemoglobin compared to both polydrug users and drug naive controls at voxel 14 pertaining to the inferior side of the right DLPFC. At voxels 2 and 16, ecstasy users had significantly smaller change in oxygenated haemoglobin relative to drug naïve controls. V2 related to the inferior side of the left DLPFC, and V16 relates to the inferior side of the right DLPFC. As such the results imply reduced activation of the dorsolateral prefrontal cortex in ecstasy users that is bilateral. A blunted decrease of deoxygenated haemoglobin in ecstasy users compared to drug naive controls V1 and relative to polydrug controls V2 and V12 are also suggestive of similar differential functioning between ecstasy users and controls over the left DLPFC area. Furthermore V12 pertains to the right medial PFC, suggesting that MDMAs effects on haemodynamic response are apparent across several areas of the PFC. In addition to these between group differences, indices of ecstasy use were significantly correlated with oxygenation change in the right and left inferior DLPFC and the inferior mid PFC. These correlations were negative, suggesting that more frequent ecstasy use, a higher lifetime dose and a larger amount used in the 30 days prior to testing were associated with a smaller oxygenation change from baseline.

In animal studies it is well documented that MDMA is a selective brain serotonin neurotoxin (Green *et al*., 2003). Moreover the DLPFC is densely innervated with 5HT neurons (Curtis & D'Esposito, 2003) and if MDMA is also a selective serotonin neurotoxin

in humans, then differential functioning of areas of the DLPFC and the cognitive processes maintained by these areas should be observable in ecstasy users. In line with this, the current results suggest a differential pattern of cognitive function in ecstasy users relative to controls that relate to areas of the DLPFC. Similar findings from other neuroimaging studies have also suggested impairment in ecstasy users that are localised to areas of the PFC. Jager *et al*. (2008) observed altered brain activity patterns in relation to associative learning in the left DLPFC as well as the right middle occipital gyrus in an fMRI study. Although, it was conceded that this does not necessarily signify serotonergic neurotoxicty, it does, however, go some way to substantiating the idea of widespread loss of serotonin axons with repeated use of MDMA. Moreover, serotonergic modulation of the DLPFC has been observed in a tryptophan depletion study with fMRI (Evers *et al*., 2005), where it was observed that behavioural reversal after tryptophan depletion was accompanied by changes in signals presenting from the right ventro medial PFC, as well as the dorsomedial prefrontal cortex. More recently Bosch et al. (2013) have linked brain glucose metabolism in the dorsolateral prefrontal cortex (DLPFC) to level of MDMA use, with higher use being associated with lower levels of glucose metabolism. MDMA users had dysfunction in glucose metabolism in a range of brain areas which is consistent with serotonergic neurotoxicity; specifically the decreases in the raphe nuclei, where serotonergic neurons stem from, provide corollary evidence of neurotoxicity/short term degradation.

This suggests that performance on cognitive tasks can be altered by transient depletion of serotonin in brain regions, such as the DLPFC that relate to higher level cognitive tasks, such as reversal learning.

Other support for serotonergic neurotoxicity following ecstasy use in humans comes from Kish *et al*. (2010) who report significantly decreased serotonin transporter binding in all cerebral cortices and the hippocampus and the decrease related to amount of drug use.

Similar decreases in SERT binding in ecstasy users were reported by Erritzoe *et al*. (2011) in a PET study. Moreover Benningfield and Cowan (2013) reviewed recent studies in to brain imaging in ecstasy users and concluded that recreational ecstasy use in humans is associated with increases in the 5HT-2A receptors and decreases in SERT. These findings suggest the neurotoxic potential of ecstasy, and given that behavioural studies have reported performance deficits in executive functioning tasks that are maintained by areas highly populated with 5HT neurons, evidence is growing to suggest possible serotonergic neurotoxicity in the prefrontal cortex. This idea is further corroborated by the current study, with the observation of a differential pattern of functioning in these areas in ecstasy users. It is important to note that the direction of oxygenation change is not as predicted. One possible reason for this may be related to the sympathomimetic effect of ecstasy. A number of previous studies have noted increased vasoconstriction in human ecstasy users not only while on drug, but for prolonged periods of abstinence. Chang *et al.* (2000) found protracted vasoconstriction evidenced by decreases in regional cerebral blood flow (rCBF) in dorsolateral areas of the PFC. In addition, Reneman *et al*. (2000) noted that reduced serotonergic binding in a SPECT study was significantly correlated with rCBF, with *low* CBF (indicating vasoconstriction) associated with *low* binding. Taussky *et al.* (2012) found a strong linear relationship between fNIRS measurements and rCBF measurements taken via perfusion CT scanning suggesting that fNIRS measurements may be sensitive to the same changes in neuromicrovasculature. Taken together, one possible reason for the reduction in oxygenation in ecstasy users is that damage to the serotonin system has caused prolonged vasoconstriction resulting in decreased rCBF in frontal areas. Consequently the change in oxygenation is less pronounced as there is less blood flow altogether.

The DLPFC is implicated in higher level cognitive functioning, and behavioural studies have shown that ecstasy users' performance on tasks that load on higher level

executive functions such as memory updating is reduced relative to controls (Montgomery & Fisk, 2008). Moreover ecstasy related cognitive deficits have been observed to be increased with task/cognitive load (Fisk *et al.,* 2011). As such the current study is in line with previous findings of ecstasy users showing cognitive deficits with increased workload, as the multitasking paradigm loads heavily on cognitive functions and alterations to normal functioning of areas of the DLPFC have been observed. The Multitasking Framework used in the present study required participants to perform several demanding cognitive tasks simultaneously. It has been shown to elicit subjective stress in nonusers (Wetherell and Sidgreaves, 2005). To further support this, Wetherell et al. (2012) found that recreational Ecstasy/MDMA users perceive significantly greater time pressure and levels of mental effort compared to non-user controls, during the multitasking framework. It is also noteworthy that 7 of the 8 participants' data that was excluded from analysis of the Stroop task module, due to incorrect interpretation of instructions were drug users (4 ecstasy users). It has been observed previously that ecstasy users made more errors when completing a web based questionnaire (Rodgers *et al.,* 2003) than other drug users and drug naïve controls. Therefore it is possible that there are deficits in the processing of instructional information associated with ecstasy use.

Functional near infrared spectroscopy, due to its specificity to the pre frontal cortex, is useful for studies in ecstasy users as it is these frontal structures that are densely innervated with 5HT neurons and are perhaps most susceptible to degradation with ecstasy use. However the level of demand and relatively high mental workload involved in the multi-tasking paradigm could require recruitment of additional brain areas that are currently not monitored with this device (Ayaz, *et al.,* 2012). Perhaps if this equipment enabled coverage of the whole brain, or indeed it was accompanied by other neuroimaging techniques such as fMRI a better

understanding of the underlying mechanisms could be achieved. Future research should seek to clarify the nature of these changes in the brain, in the absence of behavioural differences.

Although there are significant findings in the current study in relation to ecstasy users' cerebral blood flow, as with any study pertaining to cognitive deficits and ecstasy use certain limitations require a degree of caution when interpreting results. Attempts were made to control for use of other drugs with an inclusion of a polydrug user group (namely cannabis users) that were ecstasy naïve. However, the ecstasy group used a range of other drugs and as such it is still possible that any observed differences could be attributable to other drug use, or perhaps concomitant use of other drugs with ecstasy. Nevertheless, the results from pairwise comparisons did show a differential pattern of DLPFC activation in ecstasy users compared to both control groups, which suggests cognitive impairment is observable in ecstasy using populations. It should also be noted that while the multitasking framework is a good task for eliciting high mental effort and psychological/psychobiological indices of stress, multitasking as a function may be less reliant on 5HT compared to other cognitive functions such as verbal recall (Robbins & Arnsten, 2009). Future research should seek to investigate fNIRS parameters of performance utilising verbal recall tasks.

The necessity of a quasi-experimental design in this study can also be considered a limitation and the possibility that some other individual differences, besides drug use, may be responsible for the effects observed here cannot be ruled out (although, we have attempted to control for many of these, including fluid intelligence and perceived workload). Furthermore, self reports of background drug use are problematic due to recall of quantities and frequencies etc. not being entirely accurate, not least given the implications for memory deficits with drug use. However due to the legal status of the drug being investigated, this is the most appropriate method for attaining an estimate of lifetime drug use and is the most commonly used method in the literature investigating drug use and cognition (Fox *et al.*,

2001; Montgomery *et al.*, 2005; Montgomery *et al.*, 2010). Additional uncertainty about purity of ecstasy tablets consumed, as well as cocaine purity and cannabis strength cannot be assured. However, ecstasy tablets collected from amnesty bins in nightclubs in the UK have been reported to be approaching 100% purity (Parrott, 2004). Nevertheless if this is incorrect and the purity is, in fact, much lower, then perhaps magnitude of cognitive effects observed is even more concerning (Montgomery *et al.*, 2010). In the present study, resources limited us to subjective confirmation of drug use and abstinence, and we concede that an objective measure would be advantageous (e.g. from hair or urine samples). Reliance on self-report measures of drug use is common in this field of research, and there are many published studies that do not report objective measures (e.g. Fox et al, 2002; Montgomery et al. 2005; Rodgers, 2000). A comparison of subjective vs. objective measures of drug use (Scholey et al., 2011) has recently shown that self-reports of ecstasy use are consistent with objective analysis of hair samples in ecstasy users. More recently, research from our own laboratory suggests that participants are adhering to our inclusion criteria of drug abstinence (Roberts et al., 2013a; Roberts et al., 2013b); very low levels of metabolites were found in the urine of recent users and excluding these participants from analysis did not affect the results. Thus while we have no reason to believe that sub-acute intoxication would affect the results of the present study, future research should seek to utilise an objective measure of drug use

The present study provides evidence of aberrant neural functioning, in ecstasy polydrug users, in relation to DLPFC oxygenated and deoxygenated haemoglobin. Reductions in the increase of oxygenated haemoglobin to the inferior right DLPFC, as well as left inferior DLPFC, during a task that requires a high mental workload suggest that ecstasy users have changes in these networks that support higher level cognitive functioning. These changes may be attenuating any observable behavioural differences. These findings are in

line with the literature suggesting such changes in blood flow may be due to serotonergic neurotoxicity in forebrain structures.

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Table 1 –Fluid intelligence and mood variables

	Ecstasy Users		Polydrug		Drug Naïve	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Ravens Progressive Matrices (N^{o} correct: maximum 60)	49.70	5.12	51.82	5.42	49.58	6.94
SAIVAS pre calm	63.80	24.25	84.06	10.29	79.00	19.44
SAIVAS post calm	70.00	17.27	74.24	30.68	78.37	20.28
SAIVAS pre tense	20.30	15.89	15.71	19.09	16.14	16.84
SAIVAS post tense	25.10	15.97	22.35	24.89	14.32	16.24
SAIVAS pre upset	11.70	9.59	14.65	23.17	11.00	11.69
SAIVAS post upset	12.50	9.55	8.00	9.97	10.37	10.65
SAIVAS pre relaxed	66.05	20.35	68.29	28.76	79.47	16.52
SAIVAS post relaxed	64.30	17.93	69.00	29.54	78.89	16.70
SAIVAS pre content	71.60	16.54	76.76	21.33	74.21	24.67
SAIVAS post content	71.25	11.84	82.00	14.90	73.89	21.21
SAIVAS pre worried	22.40	17.27	19.12	24.76	14.79	17.69
SAIVAS post worried	19.70	12.68	13.71	17.75	12.37	13.80

Table 2: Indices of drug use.

	Ecstasy user			Polydrug			Drug Naive		
	Mean	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
Ecstasy									
Frequency	0.22	0.21	20	-	-	-	-	-	-
Last 30 days	2	3.42	20	-	-	-	-	-	-
Total use	253.86	376.20	20	-	-	-	-	-	-
Cannabis									
Frequency	2.74	2.81	20	1.11	1.56	16	-	-	-
Last 30 days	46.56	59.89	17	19.34	46.36	16	-	-	-
Total use	3613.80	4469.70	20	1562.96	3021.05	17	-	-	-
Cocaine									
Frequency	0.06	0.08	2	0.05	0.06	2	-	-	-
Last 30 days	0.00	0.00	2	0.00	0.00	2	-	-	-
Total use	415.00	43.84	2	7.50	0.71	2	-	-	-
Ketamine									
Frequency	0.19	0.19	5	-	-	-	-	-	-
Last 30 days	0.00	0.00	5	-	-	-	-	-	-
Total use	21.72	16.90	5	-	-	-	-	-	-
Mephedrone									
Frequency	0.21	0.16	4	0.16	0.27	3	-	-	-
Last 30 days	0	0	4	0	0	3	-	-	-
Total use	63.45	57.60	4	23.67	17.39	3	-	-	-
Amphetamine									
Frequency	0.13	0.09	3	0.04	-	1	-	-	-
Last 30 days	0	0	3	0	0	1	-	-	-
Total use	14.00	9.64	3	55	-	1	-	-	-
Alcohol units p/w	13.20	6.68	20	12.44	9.70	16	6.99	8.14	19

Frequency: times per week.

Units of total use and recent use (last 30 days): ecstasy (tablets); cannabis (joints); Cocaine, amphetamine, ketamine, mephedrone (grams); Alcohol (UK units).

Table 3: Performance Data (mean and SD) for the 4 tasks.

	Ecstasy users	Polydrug controls	Drug naïve controls
Stroop	4443.75 (1653.38)	4222.14 (1683.38)	4500.28 (2545.14)
Warning	550.50 (43.71)	566.47 (28.93)	533.16 (141.07)
Tracking	392.80 (112.39)	437.29 (58.23)	386.11 (203.88)
Maths	414.35 (235.65)	463.65 (230.06)	371.05 (293.16)
Total	5847.75 (1721.07)	5691.29 (1727.09)	6382.22 (2357.42)

Table 4: Correlations with indices of drug use.

	Ecstasy			Cannabis			Cocaine	
	Freq	**Total**	**Recent**	**Freq**	**Total**	**Recent**	**Freq**	**Total**
oxyV1	-.09	-.16	.03	-.17	-.03	.11	.16	.06
oxyV2	-.33*	-.36*	-.35*	-.17	-.14	-.02	.17	.05
oxyV3	-.19	-.26	-.15	-.14	-.01	.14	.11	.06
oxyV4	-.32	-.22	-.49*	.00	.12	.13	.17	.10
oxyV5	-.15	-.19	-.17	-.26	-.12	-.00	.11	.03
oxyV6	-.34*	-.42*	-.29	-.13	-.10	.08	.21	.02
oxyV7	-.08	-.10	-.11	-.02	.07	.14	.02	-.03
oxyV8	-.41*	-.45*	-.34*	-.33*	-.26	-.07	.25	.10
oxyV9	-.16	-.17	-.19	-.17	-.10	.06	.09	.05
oxyV10	-.26	-.27	-.26	-.27	-.12	-.07	.28	.20
oxyV11	-.02	-.11	-.04	-.07	.09	.04	.24	.26
oxyV12	-.29	-.33	-.33	-.24	-.11	-.10	.23	.18
oxyV13	-.12	-.17	-.08	-.08	.05	.15	.12	.13
oxyV14	-.42*	-.45*	-.38*	-.27	-.14	-.09	.34*	.11
oxyV15	-.07	.14	-.09	-.06	.14	.10	.25	.28
oxyV16	-.32	-.37*	-.32*	-.21	-.11	-.04	.21	.02
deoxyV1	-.06	-.06	-.24	.18	.24	.02	.05	.02
deoxyV2	-.11	-.19	-.21	.07	.09	-.00	-.08	-.15
deoxyV3	.19	.17	.01	.29	.21	.14	-.13	-.20
deoxyV4	.02	.07	-.14	.26	.17	.11	-.11	-.17
deoxyV5	-.01	.01	-.08	-.07	-.04	-.12	-.05	-.07
deoxyV6	-.14	-.18	-.17	.00	-.04	.10	-.07	-.40
deoxyV7	.12	.09	-.04	.20	.24	.10	-.07	-.40
deoxyV8	.12	.16	-.04	.23	.20	.15	-.08	-.03
deoxyV9	-.04	-.07	-.21	.07	.05	-.04	-.06	-.05
deoxyV10	.00	.02	-.06	.04	.14	.05	.05	.09
deoxyV11	-.15	-.07	-.10	.04	-.01	-.01	.11	.04
deoxyV12	.21	-.25	-.10	-.10	.10	-.03	.26	.30
deoxyV13	.17	-.11	-.22	.03	-.01	.00	-.03	-.05
deoxyV14	-.29	-.35*	-.27	-.16	-.08	-.13	.23	.07
deoxyV15	-.17	-.15	-.19	.02	.02	-.03	.05	.15
deoxyV16	-.09	-.13	-.20	-.05	.04	-.06	.04	.13

*Correlation significant at p<.01.

Figure 1: Mean oxy-Hb change (µmolar) from baseline during multitasking

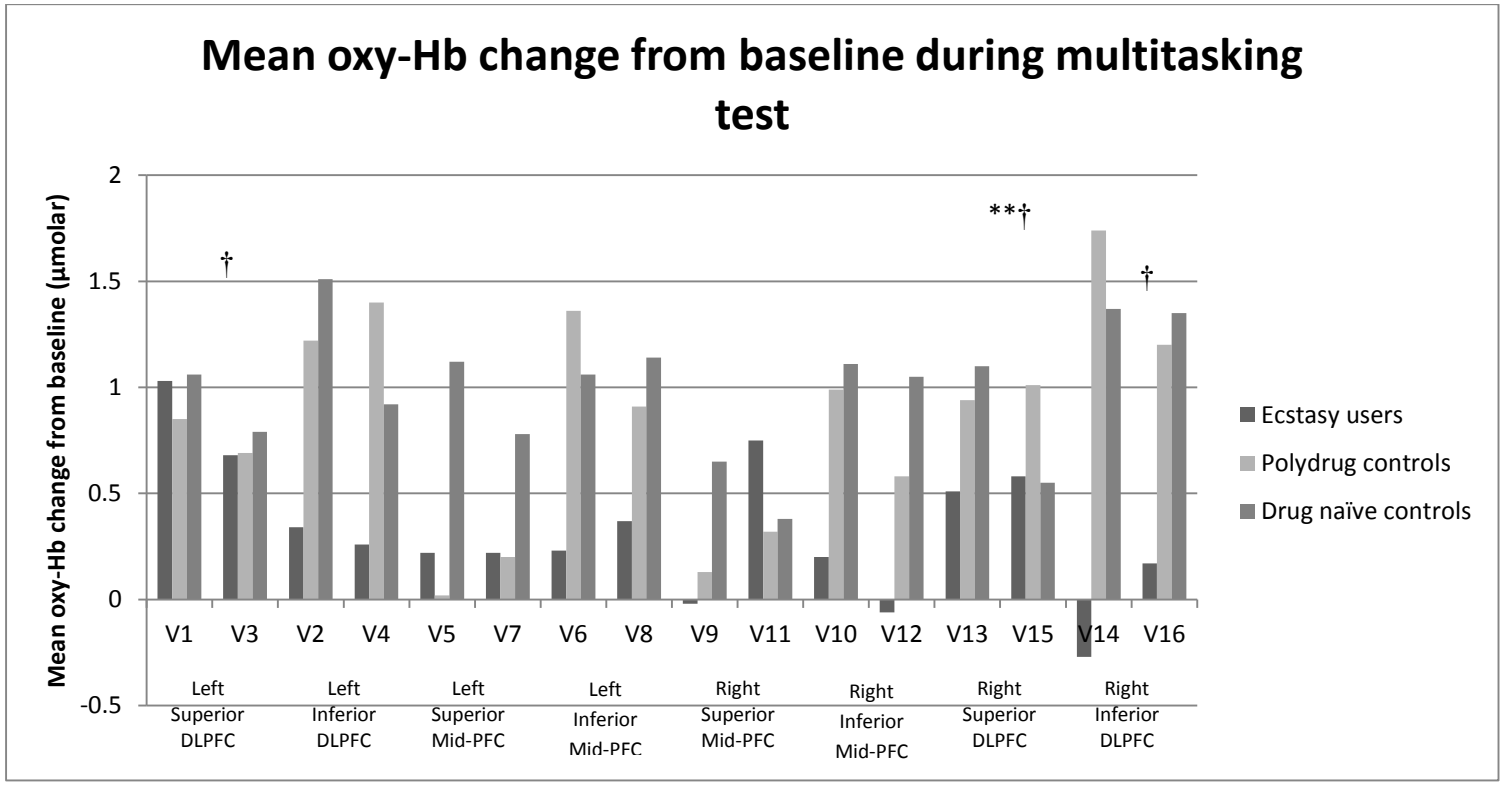

Fig.1: Depicts mean oxy-Hb change (µmolar) from baseline during the entire multitasking epoch (20 min) for ecstasy users, polydrug controls and drug naïve controls. *Indicates a significant difference from polydrug controls at the .05 level, and ** at the .01 level; † indicates a significant difference from drug naïve controls at the .05 level and †† at the .01 level.

Figure 2: Mean deoxy-Hb change (μolar) from baseline during multitasking

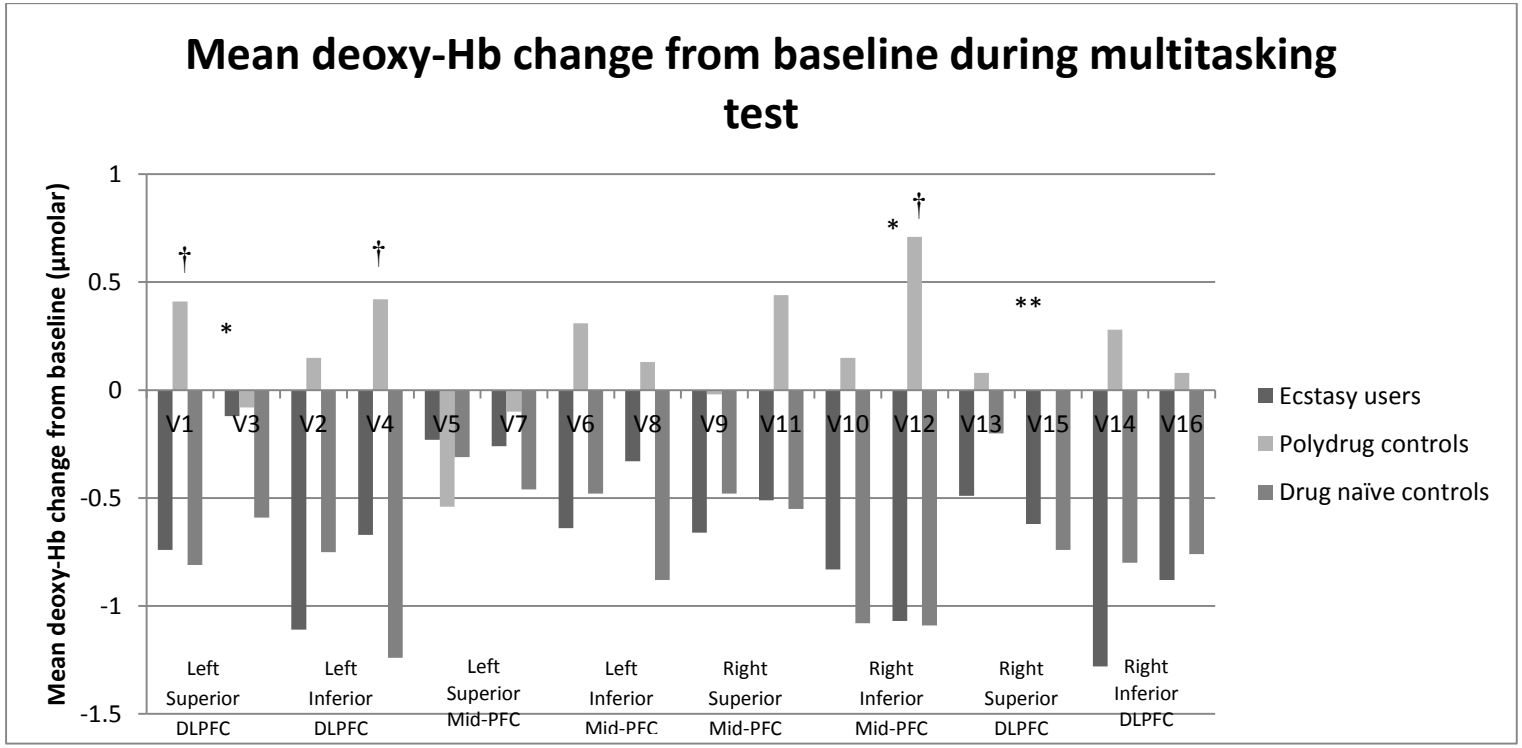

Fig.2: Depicts mean deoxy-Hb change (μmolar) from baseline during the entire multitasking epoch (20 min) for ecstasy users, polydrug controls and drug naïve controls. *Indicates a significant difference from polydrug controls at the .05 level, and ** at the .01 level; † indicates a significant difference from drug naïve controls at the .05 level and †† at the .01 level.