fNIRS suggests increased effort during executive access in ecstasy polydrug users

Running Head: executive dysfunction in ecstasy users

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Abstract

Background: Ecstasy use is associated with cognitive impairment, believed to result from damage to 5-HT axons. Neuroimaging techniques to investigate executive dysfunction in ecstasy users provide a more sensitive measure of cognitive impairment than behavioural indicators. The present study assessed executive access to semantic memory in ecstasy polydrug users and nonusers. *Methods:* Twenty ecstasy polydrug users and 20 non-user controls completed an oral variant of the Chicago Word Fluency Test (CWFT), whilst the haemodynamic response to the task was measured using functional Near Infrared Spectroscopy (fNIRS). *Results:* There were no between group differences in many background measures including measures of sleep and mood state (anxiety, arousal, hedonic tone). No behavioural differences were observed on the CWFT. However there were significant differences in oxy-Hb level change at several voxels relating to the left DLPFC and right medial PFC during the CWFT, indicating increased cognitive effort in ecstasy users relative to controls. Regression analyses showed that frequency of ecstasy use, total lifetime dose and amount used in the last 30 days were significant predictors of oxy-Hb increase at several voxels after controlling for alcohol and cannabis use indices. *Conclusion:* The results suggest that ecstasy users show increased activation in the PFC as a compensatory mechanism, to achieve equivalent performance to non-users. These findings are in agreement with much of the literature in the area which suggests that ecstasy may be a selective serotonin neurotoxin in humans.

Introduction

Ecstasy (MDMA/3,4-methylenedioxymethamphetamine) remains a popular recreational drug, with 3.3% of 16-24 year olds in the UK reporting use in the last year (Crime Survey of England and Wales, 2013), and lifetime prevalence across Europe remaining at around 7% for all age groups (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2013). Its popularity is of concern given the negative psychological and physiological consequences associated with continued use, that may have real world functional significance.

The increase in the monoamines serotonin, dopamine and norepinephrine after administration are the primary cause of its acute psychological and physiological effects (McDowell & Kleber, 1994). After regular use, down regulation of serotonin receptors may be seen in humans, similar to that proposed in animal models (Reneman *et al.*, 2002). More chronic continued use can cause serotonergic neurotoxicity, which may be long lasting. Evidence from SPECT studies reporting upregulation of 5-HT_{2A} receptors following chronic use, suggests that the brain is attempting to compensate for loss of receptors due to neurotoxicity (Di Iorio *et al.*, 2012; Reneman *et al.*, 2002; Urban *et al.*, 2012). Animal literature has provided evidence for MDMA related neurotoxicity (Molliver *et al.*, 1990; Ricaurte *et al.*, 1988). Furthermore, in humans, several studies suggest alterations to serotonergic functioning as a result of ecstasy use, for example SERT binding ratios are regularly observed to show alterations in ecstasy users relative to controls (Reneman, Booij *et al*., 2000; Reneman, Habraken *et al.*, 2000).

Various executive tasks regularly yield little evidence for ecstasy related deficits, for example the Wisconsin Card Sorting Task (Fox *et al*., 2001; Back-Madruga *et al*., 2003), whereas others more consistently show evidence of diminished performance, such as the

computation span task (Fisk *et al*., 2004). This inconsistency was explored by Montgomery *et al.* (2005), using Miyake *et al.*'s (2000) conceptual framework of executive functioning, along with the additions made by Fisk and Sharp (2004), finding that updating and access to semantic memory were affected by ecstasy use. Access describes the efficiency with which words and semantics can be retrieved from long term memory. Damage to frontal regions produces significant impairment to word fluency ability (Stuss *et al.*,1998). In ecstasy users, fluency is significantly impaired using the Chicago Word Fluency Test (CWFT) (Montgomery *et al.*, 2005), and this was more pronounced with increased difficulty. Ecstasy users have also shown deficits on a composite measure of word fluency (Montgomery *et al.*, 2007), verbal and semantic fluency (Heffernan *et al.*, 2001), and access performance compared to cannabis users and controls after controlling for differences in sleep (Fisk & Montgomery, 2009). Conversely, an oral word fluency task (Controlled Oral Word Association Task - COWAT) has been less consistent in producing ecstasy related deficits. Several studies have reported no observable differences between ecstasy users and controls using this measure (Bedi & Redman, 2008; Halpern *et al*., 2004; Halpern et al., 2011; Morgan *et al.*, 2002). However Bhattacharay and Powell (2001) observed ecstasy related deficits using the COWAT, and Croft *et al.* (2001) observed differences between a combined drug user group and controls on the semantic fluency measure of the task, whereby participants were asked to recall as many 'animals' as possible in one minute. However the authors suggest that the deficits may be more related to cannabis use than ecstasy use after covariate analysis.

One possible explanation as to why deficits are more consistently reported in the CWFT than the COWAT is that the CWFT involves production of words over 5 and 4 minute periods whereas the COWAT requires verbal responses over a one minute period. It could be that ecstasy related deficits become more apparent after long periods of sustained load on the

central executive. In addition, the more subtle cognitive deficits that result from chronic ecstasy use may not always be detectable using behavioural measures alone. Recently, neuroimaging measures have been combined with behavioural tasks, as an objective measure of performance. Roberts *et al.* (2013) observed ecstasy related alterations in cognitive processing from ERP measures during a semantic retrieval task. This study proposed that EEG correlates reflected evidence of cognitive reallocation/compensatory mechanisms in ecstasy users to perform at a similar level to controls. Furthermore this study also showed that these neurophysiological changes were a function of task difficulty. Similarly, in an fMRI study, Raj *et al.* (2010) observed BOLD signal change during a semantic recognition task in ecstasy polydrug users. There were significant correlations between ecstasy use and BOLD signal change in left BA9, 18 and 21/22 during recognition, but not encoding phases of the task. The authors suggested that these results provide evidence that semantic memory is affected by ecstasy use, despite ecstasy use not being correlated with performance. Studies such as these reflect the increased sensitivity of neuroimaging measures to detect cognitive alterations than behavioural measures alone.

fNIRS is an emerging non-invasive neuroimaging tool measuring cerebral blood flow which can be used to assess the haemodynamic response to mental demand. More specifically fNIRS uses wavelengths of light in the near infrared range to assess levels of oxygenated (oxy) and deoxygenated haemoglobin (deoxy-Hb) in the prefrontal cortex (PFC). Due to fNIRS having a penetration depth of 2-3mm (Firbank *et al*., 1998), it images relatively superficial layers of the cortex. Nevertheless, areas of the PFC are easily accessed, therefore fNIRS is ideal for observing neurological activation during tasks that load on the (Dorsolateral) PFC. Increases in oxy-Hb are accepted as reflecting an increase in neuronal activity in certain brain regions (Leff *et al*., 2011). Furthermore it is hypothesised that although blood oxygenation is expected to increase with increased workload, this is only if

the participant is engaged in the task, whereas if the task becomes too difficult and attention shifts (as well as performance decline), a decrease in oxygenation will be observed (Izzetoglu *et al*., 2004). The distribution of the activation response is regionally specific i.e. the cortical regions underlying the voxels at which the activation is observed are responsible for the activation (Leff *et al.*, 2011). Often an increase in oxy-Hb is coupled with a decrease in deoxy-Hb (Ehlis *et al.*, 2008; Leff *et al.*, 2008; Leff *et al.*, 2011). However the relationship between oxy and deoxy-Hb is non-linear and as such estimates of total blood volume are also sometimes calculated as a correlate of neuronal activation (Ayaz *et al.*, 2012).

The present study sought to investigate the cortical haemodynamic change when performing a semantic access task, in ecstasy polydrug users and non-user controls. Performance and haemodynamic response were measured on each level of the semantic task. It was hypothesized that ecstasy users would find the task more demanding than controls, shown by increased oxygenation relative to controls, but that behavioural differences would be negligible.

Method

Design:

For the CWFT, a mixed design was used with group as the between groups factor (2 levels – ecstasy user, nonuser), level of difficulty as the within groups factor (animals, S letter, C letter) and number of words produced as the dependent variables. For fNIRS analysis group with 2 levels (ecstasy user, nonuser) was the between groups variable and mean oxygenated haemoglobin change at each voxel (1-16) for each level of difficulty was the dependent variable.

Participants:

Twenty ecstasy users (mean age = 21.85±2.76; 13 = male) and 20 non-user controls (mean age = 20.89±2.05; 8 = male) were recruited via email to university students. Inclusion criteria for the ecstasy using group were: use of ecstasy on at least 5 occasions (actual minimum = 11); indices of ecstasy use were as follows: total lifetime dose 431.75 tablets ± 885.08; mean amount used in last 30 days 2.55 tablets ± 3.23, and frequency of use 0.37 times/week ± 0.51. To be included in the nonuser group, participants must have never used ecstasy; the nonuser group mainly consisted of drug naïve participants. All participants were required to be drug free for 7 days prior to testing (confirmed via self-report), and must report no current or past-year diagnosis of a psychological disorder (e.g. GAD, Major Depressive Disorder), and no current use of medications aside from the contraceptive pill and occasional non-prescription painkiller use.

Materials

Questionnaires:

Participants completed a number of questionnaires including:

Background Drug Use Questionnaire from which information about drug use (frequency of use, last 30 days use, first and last use, patterns of use) and other lifestyle variables, as well as socio-demographic variables is obtained. Using a method employed by Montgomery *et al*. (2005) estimates of total lifetime use of each drug were calculated, as well as totals for last 30 days drug use and weekly drug use estimates.

Measures of Sleep Quality:

Various questionnaires assessing alertness and sleep quality were administered to participants to investigate any potential relationship between sleep and cognition. The Epworth Sleepiness Scale (ESS; Johns, 1991) which explores the likelihood of dozing or falling asleep in various situations was used to measure subjective daytime sleepiness (high score = sleepiness). The Morningness-Eveningness Questionnaire (MEQ; Termann *et al.,* 2001) is a self-assessment of morningness-eveningness in human circadian rhythms. A high MEQ score indicates a morning type person, whereas a low score indicates and evening type person. The Karolinska Sleepiness Scale (KSS; Akerstedt & Gillberg, 1990) was used to assess sleepiness pre and post task.

Mood State:

State anxiety, arousal and hedonic tone were assessed using the scale devised by Fisk and Warr (1996). Ratings of mood on a Likert scale (1 = not at all, 5 = extremely), that relate to current mood at the time of testing were completed. A high score on each scale relates to increased hedonic tone/anxiety/arousal.

Raven's Progressive Matrices (SPM; Raven, Raven, & Court, 1998)

Ravens SPM was implemented to assess fluid intelligence. A series of problems (five sets of 12, 60 in total), are presented as a symbolic sequence. Participants must select an appropriate

response to complete the sequence from a choice of 6/8 options. Each block of 12 problems starts with an intuitively simple problem and the difficulty of the problems increases as the task progresses.

Access Task:

The Chicago Word Fluency Task (Thurstone, 1938)

This consisted of three blocks in which participants had to verbally produce as many words as they could in one minute. In the first block (semantic fluency), participants were instructed to name as many animals as they could. Following this they were instructed to produce as many words as possible beginning with the letter "S", and in the third and final block they were required to name as many four letter words beginning with the letter "C" as possible. Participants were informed that place names, people's names and plurals were prohibited. Responses were recorded on a cassette deck with a built in microphone. Scores for each of the fluency tasks were counted as the number of appropriate words in each case.

Equipment

A continuous wave fNIRS system (developed by Drexel University, Philadelphia, PA) supplied by Biopac systems (Goleta, CA, USA) was used for monitoring the haemodynamic response. A 16-channel fNIRS sensor was used with a temporal resolution of 2Hz, and a source-detector separation of 2.5cm allowing 1.25cm penetration depth (Ayaz *et al.*, 2012). An fNIR100 control box and COBI studio (Drexel university) were used for data acquisition and visualisation during data collection (as per Ayaz *et al.*, 2011; Ayaz *et al*., 2012).

Procedure

Participants attended the lab for a single session lasting approximately 2 hours. Testing sessions commenced at 9am, 11am and 1pm and 3pm, with equal numbers of each group

tested at each session time. Upon arrival participants were given an information sheet explaining what was involved in the study, and written consent was obtained. Questionnaires were administered in the following order: background drug use questionnaire, MEQ, ESS, pre-test KSS, UMACL and Raven's SPM. The fNIRS headband was then fitted to the participant's forehead (See Figure 1 for voxel anatomical locations). fNIRS signals were displayed on a desktop computer running COBI studio (Drexel University) in an adjacent room to the testing room. Once fNIRS signals were stable, a 2-minute baseline of inactivity was recorded. Participants watched a video of planet earth accompanied by soothing music and the baseline was recorded during this period. Participants then completed the CWFT. After completing the task participants were given the post task KSS. Participants were fully debriefed after the testing procedure and were 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.

fNIRS analysis

fNIRS raw data from COBI studio was pre-processed using fnirSoft (Biopac systems; Goleta, CA, USA). Saturated channels were discarded after visual inspection. A high-pass filter (0.1Hz cut off) was applied for removal of noise due to respiration and a linear phase filter (order of 20) was used to remove high frequency noise (Ayaz *et al.,* 2011; Ayaz *et al*., 2012). Oxy and deoxy-Hb changes from baseline for the 1-minute epochs measured were calculated for each of the 16 voxels using the modified Beer-Lambert law logarithm in fnirSoft (Ayaz *et al*., 2010).

Results

Socio-demographic information, sleep measures and scores of anxiety, hedonic tone and arousal are shown in Table 1. Indices of other drug and alcohol use are displayed in Table 2.

<<Insert Tables 1 & 2 Here>>

t-tests on these background variables revealed there were no significant differences between the two groups in age $t(36) = 1.21$, $p>.05$, total scores on the ESS $t(37) = -0.28$, $p>.05$, MEQ $t(30) = -.1.37$, $p>.05$, Raven's SPM $t(38) = -0.41$, $p>.05$, pre-test KSS $t(38) = -0.88$, $p>.05$, post-test KSS $t(26) = 1.59$, $p>.05$, or levels of arousal $t(38) = -0.28$, $p>.05$, hedonic tone $t(38) = 0.41$, $p>.05$ and anxiety $t(38) = -0.07$, $p>.05$. However ecstasy users did drink significantly more units of alcohol per week than non-users $t(38) = 2.71$, $p<.01$, and it is clear from Table 2 that there is concomitant drug use in this cohort.

Behavioural Data Analysis:

In the behavioural data analysis and all fNIRS analyses, gender was included as a covariate due to uneven gender distribution between the groups in the present study, and to address possible gender differences in access to semantic memory performance (Loonstra et al., 2001). Number of words produced at each level of difficulty in the CWFT is displayed in Table 3. A mixed ANOVA was conducted on the CWFT data with group as the between subjects variable and level of difficulty as the within subjects variable (in order of relative difficulty: animals < "S" letter < "C" letter), and gender as a covariate. There was a significant main effect of difficulty on the task $F(1.58, 58.59) = 17.08$, $p<.01$ (the sphericity assumption was violated so Greenhouse-Geisser adjusted stats are reported), however there was no gender by difficulty interaction $F(1.58, 58.59) = 0.09$, $p>.05$ and no group by difficulty interaction $F(1.58, 58.59) = 0.57$, $p>.05$. Furthermore there was no significant effect of group $F(1,37) = 0.22$, $p>.05$.

<<Insert Table 3 Here>>

fNIRS Analysis

Averaged oxy and deoxy-Hb changes from baseline, over the one minute epochs for each level of the task can be observed in Figures 2 and 3. A series of ANOVAs[1] were conducted to assess group differences in oxy and deoxy-Hb changes from baseline for each block of the task. Analysis of oxy-Hb change in block one of the CWFT ("animals") revealed that after controlling for gender differences, ecstasy users displayed a significant increase in oxy-Hb compared to controls at V2 $F(1,36) = 8.50$, $p<.01$, V3 $F(1,35) = 8.42$, $p<.01$, V4 $F(1,18) = 4.21$, $p<.05$, V10 $F(1,30) = 6.54$, $p<.05$, V11 $F(1,23) = 12.79$, $p<.05$ and V16 $F(1,17) = 3.96$, $p<.05$. Differences were approaching significance at V5 $F(1,36) = 7.76$, $p=.06$, V12 $F(1,32) = 3.82$, $p = .06$ and V13 $F(1,36) = 3.24$, $p = .08$. All other differences were non-significant ($p>.05$). ANOVA on the deoxy-Hb data revealed that ecstasy users showed greater deoxygenation compared to controls at V2 $F(1,36) = 5.70$, $p<.05$ and V4 $F(1,17) = 4.60$, $p<.05$. No other differences were observed for any other voxel measured ($p>.05$ in each case).

<<Insert Figure 2 Here>>

After controlling for gender, naming words beginning with the letter "S" yielded significant increases in oxy-Hb change in ecstasy users relative to controls at V3 $F(1,35) = 6.02$, $p<.05$, V4 $F(1,17) = 5.78$, $p<.05$, V10 $F(1,30) = 11.13$, $p<.01$ and V12 $F(1,32) = 3.65$, $p>.05$. This difference was also approaching significance at V2 $F(1,36) = 3.51$, $p = .06$. There were no significant between group differences at any of the other voxels measured ($p>.05$ in each case). After controlling for gender, ANOVA on deoxy-Hb change revealed ecstasy users had significantly greater deoxy-Hb at V4 $F(1,17) = 4.34$, $p<.05$, with trends at V2 $F(1,36) = 3.94$, $p = .06$ and V14 $F(1,36) = 3.51$, $p = .07$. There were no significant differences at any of the other voxels measured ($p>.05$ in each case).

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

<<Insert Figure 3 Here>>

After controlling for gender, oxy-Hb change during the most demanding block (4-letter C words) of this task revealed that ecstasy users displayed a significant increase in oxy-Hb compared to controls at V3 $F(1,35) = 4.77$, $p<.05$, V4 $F(1,17) = 5.04$, $p<.05$, V10 $F(1,30) = 9.64$, $p<.01$ and V12 $F(1,32) = 7.79$, $p<.01$. Differences approached significance at V2 $F(1,37) = 3.52$, $p=.07$. There were no significant differences at any of the other voxels measured ($p>.05$ in each case). There were no significant between group differences in deoxy-Hb change during this part of the task ($p>.05$ in all cases). However ecstasy users displayed greater deoxygenation compared to controls that was approaching significance at V2 $F(1,36) = 3.09$, $p=.08$ and V4 $F(1,17) = 3.25$, $p=.08$. There were no significant differences at any of the other voxels measured ($p>.05$ in each case).

Overall these results show a general increase in oxy-Hb from baseline for ecstasy users compared to controls that is significant at several voxels in each level of the task.

Due to the high level of cannabis and alcohol use amongst the ecstasy user group in the current sample, multiple regression analyses were conducted on the fNIRS data, at voxels showing between group differences, to observe whether ecstasy use predicted oxy-Hb level after controlling for cannabis use. Oxy-Hb (μmolar) change level was entered as the dependent variable in each case. In step one average weekly dose of alcohol use was entered, in step two indices of cannabis use were entered as predictors (frequency of use, total lifetime dose, recent use (amount taken in the last 30 days) and in step three the same indices of ecstasy use were entered as predictors. For brevity only regressions yielding significant results are reported here, and statistics associated with significant models are summarised in Table 4.

<<Insert Table 4 Here>>

For Block 1 (animals) the regressions for V2, V10 and V16 oxy-Hb and V2 deoxy-Hb were non-significant so these are not discussed further. For the regression model predicting oxy-Hb at V3, the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant, $p>.05$ in both cases. When indices of ecstasy use were added in step 3, the overall model was significant $F(7,30) = 4.16$, $p<.01$, accounting for 37.4% of the variance in oxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 18.9% of the variance). Average alcohol consumption and frequency of cannabis use emerged as significant predictors, and after removing variance due to these predictors, frequency of ecstasy use and total lifetime dose of ecstasy were significant individual predictors. For the regression model predicting oxy-Hb at V4, the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant, $p>.05$ in both cases. When indices of ecstasy use were added in step 3, the overall model was significant $F(7,19) = 6.03$, $p<.01$., accounting for 78% of the variance in oxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 54.6% of the variance). Average alcohol consumption and total lifetime dose of cannabis emerged as significant predictors, and after removing variance due to these predictors, frequency of ecstasy use and total lifetime dose of ecstasy were significant individual predictors. For the regression model predicting oxy-Hb at V11, the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant, $p>.05$ in both cases. When indices of ecstasy use were added in step 3, the overall model approached significance $F(7, 19) = 2.42$, $p = 0.06$., accounting for 48.5% of the variance in oxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 25.1% of the variance). Total lifetime dose of ecstasy was the only significant individual predictor. Finally the regression model predicting deoxy-Hb at V4 the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant,

p>.05 in both cases. When indices of ecstasy use were added in step 3, the overall model was significant F(7,19) = 7.86, p<.01, accounting for 82.1% of the variance in deoxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 74.4% of the variance). Lifetime dose of cannabis and recent cannabis use emerged as significant predictors and after removing variance due to alcohol and cannabis, lifetime dose of ecstasy was a significant individual predictor.

For block 2 of the task (S-letter words) the regressions for V10 and V12 oxy-Hb were non-significant so these are not discussed further. For the regression model predicting oxy-Hb at V3, the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant, p>.05 in both cases. When indices of ecstasy use were added in step 3, the overall model was significant F(7,30) = 4.24, p<.01, accounting for 49.7% of the variance in oxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 36.6% of the variance). Average alcohol consumption emerged as a significant predictor, and after removing variance due to this, frequency of ecstasy use and total lifetime dose of ecstasy were significant individual predictors. For the regression model predicting oxy-Hb at V4, the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant, p>.05 in both cases. When indices of ecstasy use were added in step 3, the overall model was significant F(7,19) = 5.79, p<.01, accounting for 77.2% of the variance in oxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 45.8% of the variance). Average alcohol consumption and lifetime dose of cannabis emerged as significant predictors, and after removing variance due to this, total lifetime dose of ecstasy and current use (last 30 days) were significant individual predictors. For the regression model predicting deoxy-Hb at V4, the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant, p>.05 in both cases. When indices of ecstasy use were added in step 3, the overall model was

significant $F(7,19) = 9.94$, $p<.01$, accounting for 85.3% of the variance in deoxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 73.7% of the variance). Total lifetime dose of cannabis and recent cannabis use emerged as significant predictors, and after removing variance due to this, total lifetime dose of ecstasy was a significant individual predictors.

For Block 3 (4-letter C words) the regressions for V10 and V12 oxy-Hb were non-significant so these are not discussed further. For the regression model predicting oxy-Hb at V3, the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant, $p>.05$ in both cases. When indices of ecstasy use were added in step 3, the overall model was significant $F(7,30) = 3.98$, $p<.01$, accounting for 48.1% of the variance in oxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 38% of the variance). Average alcohol consumption emerged as a significant predictor, and after removing variance due to this, frequency of ecstasy use was a significant individual predictor. For the regression model predicting oxy-Hb at V4, the overall models for step 1 (alcohol) and step 2 (alcohol and cannabis) were non-significant, $p>.05$ in both cases. When indices of ecstasy use were added in step 3, the overall model was significant $F(7,19) = 5.60$, $p<.01$, accounting for 76.6% of the variance in oxy-Hb (after removing variance due to cannabis and alcohol use, ecstasy use indices accounted for an additional significant 48.7% of the variance). Average alcohol consumption, lifetime dose of cannabis and recent cannabis use emerged as significant predictors, and after removing variance due to this, lifetime dose of ecstasy and recent ecstasy use were significant individual predictors.

The results indicate that ecstasy users consistently show significantly increased oxy-Hb relative to controls over several voxels pertaining to the left DLPFC and right medial PFC during each block of the task. Ecstasy users also displayed significant increases in deoxy-Hb

compared to controls at V2 and V4 relating to the left DLPFC and left medial PFC in blocks one (animals) and two ("s" letter words). Ecstasy use indices remained as significant predictors of oxy and deoxy-Hb in the regression analyses after removing variance due to weekly alcohol consumption and cannabis use indices, with increased ecstasy use indicating increased oxy and deoxy-Hb change from baseline. However, alcohol use and indices of cannabis use did emerge as significant predictors of Hb-change in some of the regression analyses with increased use associated with increased oxy-Hb and deoxy-Hb change.

Discussion

This study investigated ecstasy related deficits in access, using performance indices and measures of haemodynamic response in the PFC with fNIRS in a sample of ecstasy polydrug users and non-user controls. The ecstasy users in the current sample did not differ significantly from controls in fluid intelligence, sleep measures or levels of arousal, depression or anxiety. However, they did report drinking significantly more alcohol per week than controls and due to their concomitant use of other drugs, it may be more appropriate to refer to them as polydrug users.

The two groups in this study did not show performance differences at any level of the CWFT. However there were several between group differences in the fNIRS data that warrant discussion. Ecstasy users displayed increases in oxygenated haemoglobin compared to controls in three voxels relating to the left DLPFC (V2, V3, V4) as well as three voxels relating to the right medial and dorsolateral PFC (V10, V11, V16) on what is considered to be the easiest level of difficulty on the task (naming animals). In this block it should be noted that while behavioural differences were non-significant, there was a mean difference of 3.45 words with ecstasy users performing better than nonusers, so these increases in oxygenation could be facilitating better performance, albeit non-significantly. As difficulty increased,

ecstasy users displayed a significantly greater increase in oxygenated haemoglobin relative to controls at two voxels (V3, V4) relating to the left DLPFC and a further two voxels relating to the right medial PFC (V10, V12). This increase in oxygenation is complimented by an increase in deoxygenation compared to controls at V4 in the left DLPFC (and V2 that was approaching significance) and V14 in the right DLPFC that was approaching significance. In the final and most difficult phase of the task (4 letter words beginning with C) ecstasy users display significant increases in oxygenated haemoglobin compared to controls at four voxels (V3, V4, V10, V12) and a further one voxel approaching significance (V2) that pertain to the left DLPFC and right medial PFC.

Thus ecstasy users show consistently increased levels of oxygenated haemoglobin in the LDLPFC and RPFC regions during the access executive function. However, there was no observed increase in oxygenation as a function of task difficulty as shown in previous research (Montgomery *et al.*, 2005). This tentatively indicates that access to semantic memory may be an "all or nothing" process which requires a certain amount of neural resources to be activated, but this does not increase with increasing difficulty. In addition, increases in oxy-Hb to both the left and right hemispheres may reflect the need for more cognitive resources to attenuate behavioural performance decline. This is in line with previous reports from ERP (Roberts *et al.*, 2013) and fMRI (Raj *et al*., 2010) studies that indicate atypical cognitive processing in ecstasy users, despite equivalent behavioural performance during semantic retrieval. This highlights the greater sensitivity of neurophysiological measures to detect cognitive impairment. It is possible that compensatory mechanisms may explain the lack of behavioural differences observed using similar tasks in the literature (Bedi & Redman, 2008; Halpern *et al.*, 2004; Morgan *et al*., 2002), especially if we consider that these studies employed simpler word fluency measures than those yielding performance differences (e.g. Montgomery *et al*., 2005). Moreover Montgomery *et al*. (2005)

used a much longer time frame for generating words than the task employed in this study (and those in the studies mentioned above), suggesting that longer periods of sustained load on the central executive produce more pronounced effects.

The importance of measuring haemodynamic response to tasks where subjects perform at a similar level behaviourally has been explored previously in human operators (for example, air traffic control operators – Ayaz *et al.*, 2012). Such studies highlight the dissociation between cognitive effort and performance output, arguing that performance can be maintained at necessary levels via increased mental effort or perhaps strategic alterations. However increased mental workload is also predictive of future performance failure (with increased demand or task changes). Increases in oxy-Hb are accepted as increases in cognitive effort despite behaviourally similar performance, and can be used as an assessment of operators' ability (Ayaz *et al.*, 2012). Thus increasing cognitive effort to maintain similar behavioural performance may reflect recruitment of additional cognitive resources compared to controls, and predict future cognitive decline. This is likely to be more pronounced in recent users of the drug and future research should focus on investigating performance after prolonged abstinence.

It is interesting to note the consistent increase in oxy-Hb in the left DLPFC and right medial PFC over all three levels of the task, given these areas have been implicated in semantic and word fluency previously. Stuss *et al.* (1998) observed that patients with lesions to the left DLPFC showed severe impairments on letter based word fluency measures. The same lesion sites produced impairments in category based fluency, but so did lesions to right medial and DLPFC regions. Indeed the left inferior frontal gyrus, has been consistently associated with semantic and phonologic processing in functional neuroimaging studies (Costafreda *et al.*, 2006), so it is interesting that these areas should show the greatest differences in the word fluency task here. These areas show increased oxygenation indicating

increased effort in ecstasy users compared to controls to achieve similar performance. Likewise, Raj *et al*. (2010) observed that ecstasy users displayed cognitive processing aberrations that relate to areas of the DLPFC during semantic recognition, despite equivalent task performance, in an fMRI study, that is broadly consistent with the present findings.

The idea that this differential pattern of functioning in the (DL)PFC reflects potential ecstasy-related neurotoxicity warrants further discussion. These forebrain structures are densely innervated with 5-HT neurons (Curtis & D'Esposito, 2003), thus alterations to functioning in these areas would be expected after repeated use of ecstasy if it is a selective serotonin neurotoxin in humans, as it is in animals (Green, 2003). This is in line with the findings of the current study, as well as other neuroimaging studies that have observed alterations to prefrontal areas in ecstasy users (Jager *et al.,* 2008; Moeller *et al.,* 2004; Roberts & Garavan, 2010). Further to this point, the three aforementioned fMRI studies (Jager *et al.,* 2008; Moeller *et al.,* 2004; Roberts & Garavan, 2010) all observe that ecstasy users display increased neuronal activity as a compensatory mechanism to achieve similar performance as controls despite being less efficient at the task.

Curiously increases in oxy-Hb were complimented by increases in deoxy-Hb in the ecstasy user group in the current study. Moreover, increases in deoxy-Hb from baseline were significantly different from controls at V4, with trends at V2 and V14 during the second block of the task. Previous research has suggested that increases in oxy-Hb are often complimented by a decrease in deoxy-Hb in the same area (Ehlis *et al.,* 2008; Leff *et al*., 2008). However oxygenated and deoxygenated haemoglobin do not necessarily have a linear relationship, rather they are separate sources of haemodynamic response. Several studies have shown increases in deoxy-Hb alongside increases in oxy-Hb (Hoshi & Tamura, 1993; Sakatani *et al*., 1999). As such deoxy-Hb appears to be a less reliable measure of neuronal activation than oxy-Hb in fNIRS. Nevertheless these results are better understood as an

increase in total haemoglobin to the areas of the prefrontal cortex that are involved in this executive function, given that total-Hb is understood to be the sum of oxy-Hb and deoxy-Hb (Steinbrink *et al*., 2006).

It is worthy of note that while the participants in the present study reported that ecstasy was their "drug of choice", there was co-use of other drugs in the ecstasy user group. The most prominently co-used substance was alcohol with cannabis also being used by many participants. In the regression analyses, models that used alcohol alone or alcohol and cannabis were non-significant. However models including indices of ecstasy use were significant for changes in oxy- and deoxy-Hb at 9 voxels. Indices of ecstasy use were significant predictors on 14 occasions after removing any variance due to alcohol and cannabis. Nonetheless, in the 3rd step of the model, cannabis and alcohol did emerge as significant predictors on a number of occasions, lifetime dose of cannabis featured prominently in this respect. Previous research (Kiang et al., 2013) has shown that cannabis users have shown ERP abnormalities during semantic memory processing. Thus future research should seek to elucidate fully the relative roles of ecstasy and cannabis in semantic memory deficits.

Despite the significant differences between ecstasy users and controls in this study, as with any study investigating cognitive deficits in ecstasy users, the results require caution during interpretation. Due to concomitant use of other drugs, it cannot be ruled out that other drugs or alcohol either alone or in conjunction with ecstasy may be responsible for the effects observed in this study. Attempts were made to statistically control for use of the most prominent co-used substances – alcohol and cannabis, using regression analyses. After controlling for alcohol and cannabis use indices, ecstasy use indices came out as significant predictors of oxy-Hb increase at several voxels, suggesting that use of ecstasy is most likely responsible for the observed differences. However in the absence of a pure ecstasy using

sample such as that used in Halpern et al. (2011), it is difficult to attribute the observed differences in the present study solely to ecstasy so the effects is best described as an ecstasy-polydrug effect. Attempts have also been made to control for several potential confounds including fluid intelligence, sleep measures and levels of anxiety, depression and arousal, with no between group differences reported in any of these variables; however, a diagnostic psychiatric interview (e.g. the SCID) was not used in screening so future research should seek to rule out any underlying differences in psychopathology which may contribute to the observed effects. We also controlled for potential gender differences via ANCOVA, but in future, matching groups on this basis would be preferable. Self-report measures of background drug use, while frequently used in this research, may not be ideal given the implications of memory deficits associated with illicit drug use. It is also possible that substance users could lie on self-reports of drug use. However, we do not believe this to be the case in the present study as participants were not informed that they would be penalised for failing to meet these criteria. In recent work from our laboratory, a very low level of recent use was found in participants' urine. Exclusion of participants testing positive for metabolites did not change the significant effects (Roberts et al., 2013). Furthermore, self-reports of ecstasy use are consistent with objective analysis of hair samples in ecstasy users (Scholey et al., 2011), thus we believe that while objective analysis of drug metabolites is desirable, the lack of this in the present study does not detract from the main significant findings. Also, the purity of ecstasy tablets consumed, as well as cocaine purity and cannabis strength cannot be verified. However, Parrott (2004) reported ecstasy tablets collected from amnesty bins in nightclubs in the UK were approaching 100%. Nevertheless, if this is no longer the case and the purity of MDMA in tablets consumed by participants in this study is much lower, then the magnitude of cognitive effects observed is of even greater concern. In addition even in low content MDMA tablets, the presence of Methylenedioxyamphetamine

(MDA), Methylenedioxyethylamphetamine (MDEA/MDE) and other compounds usually found in street ecstasy has been found to lengthen and strengthen the effects of the drug (Bexis & Docherty, 2006).

The present study provides evidence of altered neuronal functioning in ecstasy polydrug users relative to controls during a task that taps the executive function of access. Significant increases in oxy-Hb over areas of the left DLPFC and right medial PFC during all levels of the task were observed in ecstasy users relative to controls that reflect compensatory mechanisms/recruitment of additional resources to achieve similar performance. These results suggest that ecstasy users are engaged in more effortful cognition than non-users, perhaps due to damage to the serotonergic system.

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

	Ecstasy users	**Non-users**
Males: n, (%)	13 (65)	8 (40)
Age (SD)	21.85 (2.76)	20.89 (2.05)
University degree: n (%)	4 (20)	5 (25)
Employment status		
Student; n, (%)	17 (85)	20 (100)
Employed; n (%)	2 (10)	0 (0)
Unemployed; n (%)	1 (5)	0 (0)
	Mean (SD)	**Mean (SD)**
Ravens Progressive Matrices (maximum 60)	47.20 (5.64)	48.00 (6.79)
ESS Score (maximum 24)	5.00 (2.81)	5.25 (2.81)
KSS before	4.30 (1.49)	4.75 (1.74)
KSS after	5.33 (2.15)	4.06 (2.05)
MEQ total	45.33 (9.31)	50.00 (9.95)
UWIST anxiety	8.70 (2.56)	8.75 (2.24)
UWIST depression	9.05 (3.22)	8.70 (2.00)
UWIST arousal	17.35 (5.38)	17.75 (3.29)
Weekly alcohol use (UK units)	18.68(11.91)	9.75(8.63)

Table 2: Indices of drug use

	Ecstasy users			Nonusers		
	Mean	**SD**	**N**	**Mean**	**SD**	**N**
Cannabis						
Frequency (times/wk)	1.42	1.94	19	0.04	-	1
Last 30 days (joints)	23.03	40.19	19	1	-	1
Total use (joints)	1607.88	2212.54	19	2		1
Cocaine						
Frequency (times/wk)	1.15	2.96	11			
Last 30 days (lines)	6.42	6.42	12			
Total use (lines)	294.64	294.64	14			
Ketamine						
Frequency (times/wk)	0.24	0.32	10			
Last 30 days use (grams)	0.33	0.71	9			
Total use (grams)	7.16	9.56	11			
Abstinence (weeks)						
Ecstasy	17.40	29.96	20			
Cannabis	21.25	71.55	19	2	-	1
Cocaine	16.00	28.49	14			
Ketamine	27.57	31.30	11			
LSD	101.60	104.79	5			
Ever used (N)						
Cannabis			19			
Cocaine			14			
Ketamine			11			
LSD			5			
Poppers			10			
Viagra			2			

Table 3: Means and SDs for CWFT scores for ecstasy users and non-users

	Ecstasy users Mean (SD)	*Non-users* Mean (SD)
CWFT		
Animals	42.10 (9.24)	38.55 (7.27)
Words beginning with "S"	37.95 (11.26)	35.75 (11.49)
4 letter words beginning with "C"	15.45 (7.12)	15.55 (8.17)

Table 4: Summary of Regression analyses.

Dependent	Model	R^2%	Predictor	β	t	p
Animals:						
V3OxyHb	1	7.2	Average alcohol	-0.53	-3.31	<.01
	2	18.5	Cannabis frequency	0.42	2.46	<.05
	3	37.4	Ecstasy frequency	0.55	3.25	<.01
			Lifetime dose ecstasy	0.38	2.16	<.05
V4OxyHb	1	6.1	Average alcohol	-0.88	-3.71	<.01
	2	20.3	Lifetime dose cannabis	0.77	3.31	<.01
	3	78.0	Ecstasy frequency	0.45	2.21	<.05
			Lifetime dose ecstasy	0.50	3.53	<.01
V11OxyHb	1	5.4	Lifetime dose ecstasy	0.52	2.95	<.01
	2	23.4				
	3	48.5				
V4 deoxyHb	1	0	Lifetime dose cannabis	0.47	2.22	<.05
	2	7.7	Recent Cannabis Use	-0.75	-2.35	<.05
	3	82.1	Lifetime dose ecstasy	0.90	7.02	<.001
S-Letter:						
V3OxyHb	1	5.7	Average alcohol	-0.54	-3.38	<.01
	2	13.1	Ecstasy frequency	0.51	2.99	<.01
	3	49.7	Lifetime dose ecstasy	0.49	2.83	<.01
V4OxyHb	1	0.4	Average alcohol	-0.87	-3.63	<.01
	2	31.4	Lifetime dose cannabis	1.14	4.79	<.01
	3	77.2	Lifetime dose ecstasy	0.46	3.16	<.01
			Recent Ecstasy Use	1.14	3.62	<.01
V4deoxyHb	1	0.1	Lifetime dose cannabis	0.63	3.30	<.01
	2	11.6	Recent Cannabis Use	-0.72	-2.53	<.05
	3	85.3	Lifetime dose ecstasy	0.89	7.73	<.001
C-Letter						
V3OxyHb	1	3.3	Average alcohol	-0.57	-3.52	<.01
	2	7.1	Ecstasy frequency	0.60	3.49	<.01
	3	48.1				
V4OxyHb	1	0.7	Average alcohol	-0.96	-3.94	<.01
	2	27.9	Lifetime dose cannabis	1.19	4.94	<.001
	3	76.6	Recent Cannabis Use	-1.25	-3.44	<.01
			Lifetime dose ecstasy	0.37	2.56	<.05
			Recent Ecstasy Use	1.32	4.12	<.001

Figure 1: Anatomical locations of fNIRS channels in relation to prefrontal cortex.

Reproduced from Kreplin & Fairclough (2013) with permission.

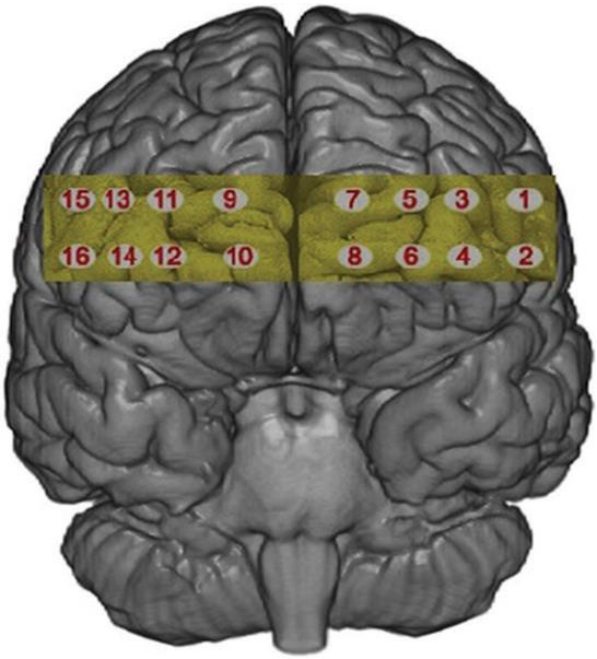

Figure 2: Mean oxy-Hb change (μolar) from baseline during the task.

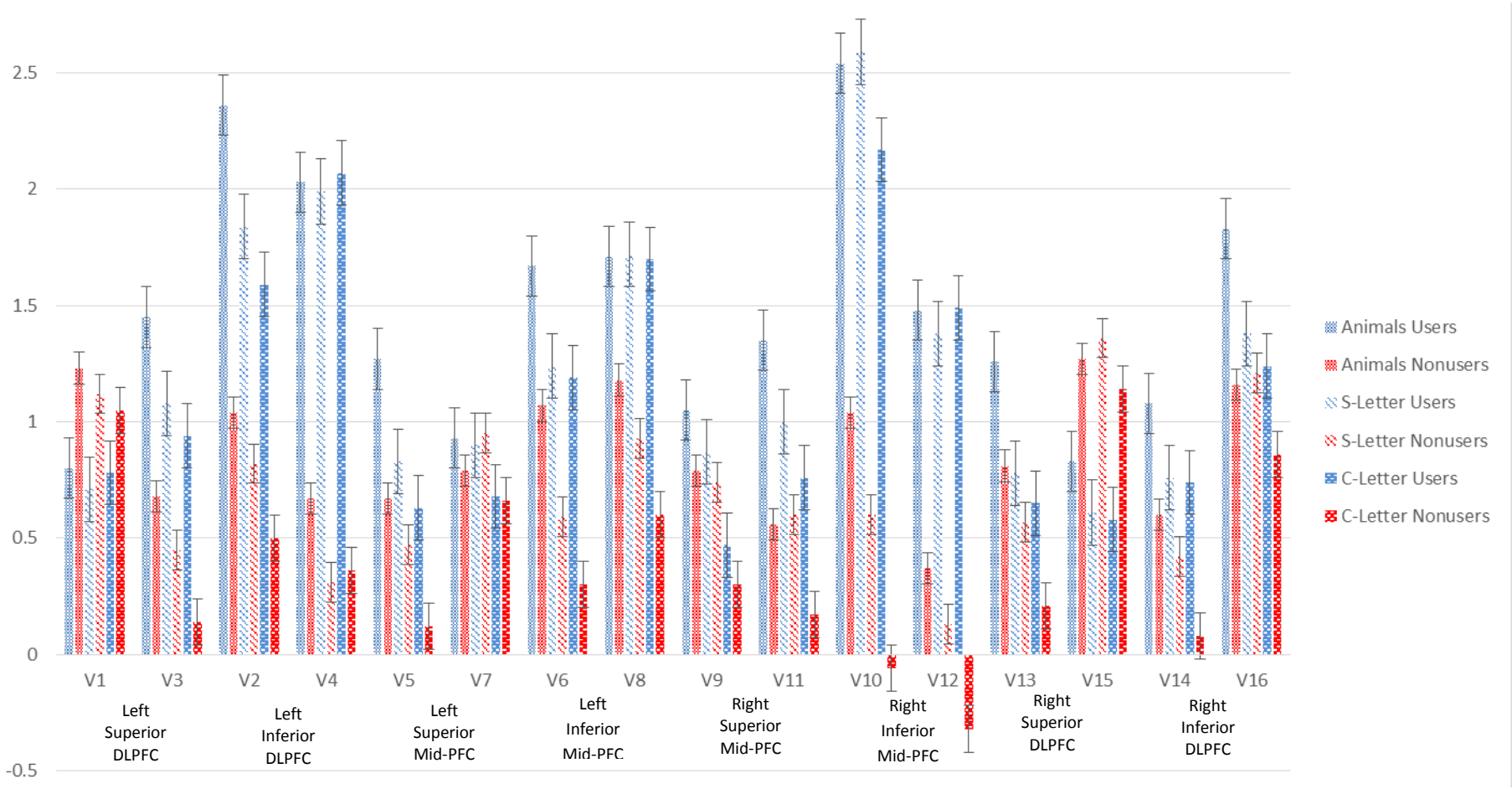

Fig 2: Depicts mean oxy-Hb change (μmolar) from baseline during the CWFT for ecstasy users and non-users, with standard error bars.

Figure 3: Mean deoxy-Hb change (µolar) from baseline during the task.

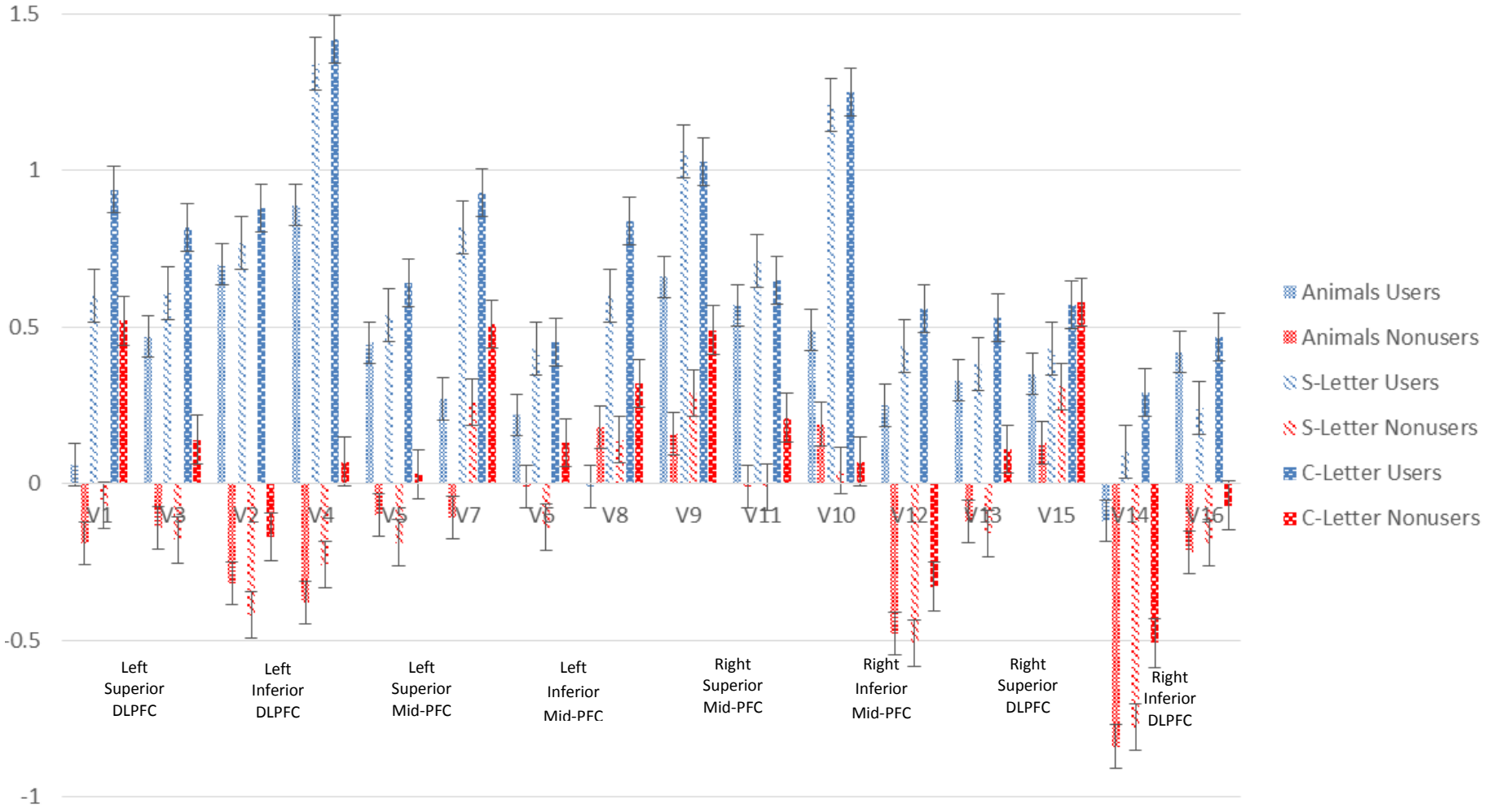

Fig.3: Depicts mean deoxy-Hb change (µmolar) from baseline during the CWFT, with standard error bars.