Electrophysiological indices of altered working memory processes in long-term ecstasy users

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Objective The aim of this study was to determine the effect of light long-term ecstasy consumption on verbal short-term and working memory and to identify the cognitive processes contributing to task performance.

Method Electroencephalogram was recorded while ecstasy users (N = 11), polydrug users (N = 13), and non-users (N = 13) completed forward and backward serial recognition tasks designed to engage verbal short-term memory and verbal working memory, respectively.

Results All three groups displayed significantly lower digit-backward span than digit-forward span with ecstasy users displaying the greatest difference. The parietally distributed P3b was significantly smaller in the digits backward task than in the digits forward task in non-ecstasy-using controls. Ecstasy users did not show the reduced P3b component in the backward task that was seen in both non-ecstasy-using control groups.

Conclusions Ecstasy users’ performance was suppressed more by the concurrent processing demands of the working memory task than that of the non-ecstasy-using controls. Non-ecstasy-using controls showed differential event-related potential wave forms in the short-term and working memory tasks, and this pattern was not seen in the ecstasy users. This is consistent with a reduction in the cognitive resources allocated to processing in working memory in ecstasy users. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—ecstasy; short-term memory; working memory; event-related potentials; P3b

Ecstasy is an illicit recreational drug, which acts on the brain by promoting the release and blocking the reuptake of serotonin (Morton, 2005). Acutely, ingestion of ecstasy induces feelings of euphoria, energy, and increased connection with others, whereas extended use has been associated with altered sleep, changed appetite, increased anxiety, and paranoia (Morgan, 2000, Parrott, 2001, Dumont and Verkes, 2006). Long-term ecstasy consumption has been linked to serotonergic dysfunction by nuclear imaging studies, post-mortem examination, and serotonin agonist studies (Kish et al., 2000, Ricaurte et al., 2000, McCann et al., 2005, Cowan, 2007).

Consistent with the role of serotonin in memory processes (Luciana et al., 2001), serotonergic dysfunction resulting from ecstasy use has been proposed as a mechanism responsible for the link between ecstasy consumption and impaired memory function. Quantitative reviews of studies examining long-term ecstasy users’ memory performance have found that ecstasy use has a significant negative effect on short-term memory. (Verbaten, 2003, Laws and Kokkalis, 2007) and working memory performance (Nulsen et al., 2010a). Short-term memory is responsible for retention and retrieval of unprocessed information. In contrast, working memory refers to a limited capacity system responsible for the active maintenance, concurrent processing, and retrieval of task-relevant processed information (Richardson, 2007). A meta-analytic review found a significant relationship between lifetime ecstasy consumption (LITEC) and effect size in working memory ($r = 0.49$, $p = 0.01$) but not in short-term memory ($r = -0.07$, $p = 0.67$) (Nulsen et al., 2010a). This relationship showed that greater LTEC was associated with greater impairment in working memory performance, which suggests that the negative effects of ecstasy consumption on working memory are cumulative and irreversible.

Ecstasy users’ performance on working memory tasks relative to non-ecstasy-using controls is sensitive to memory load, meaning that ecstasy users’ performance is more negatively affected by increasing the number of stimuli that must be retained for successful task completion than that of non-ecstasy-using controls. N-back tasks engage working memory by requiring updating of a set of stimuli held in memory. Memory recall...
load is manipulated by changing the size of the set of stimuli held in memory. Ecstasy users showed unimpaired performance on n-back tasks with low memory loads of one or two stimuli (Daumann et al., 2003a, Daumann et al., 2003b). However, when performing working memory tasks requiring updating of high memory loads, where the set of stimuli was six or the maximum span obtained on a simple span task, ecstasy users showed significantly impaired performance relative to non-ecstasy-using controls (Fisk and Montgomery, 2009). The unimpaired performance shown by ecstasy users on the low memory load tasks is likely to be because the tasks are not sufficiently taxing on memory function to show a difference between ecstasy users and non-ecstasy-using controls. The ecstasy-related impairments seen on high memory load tasks show that ecstasy use leads to impaired performance on tasks that require updating large sets of stimuli held in memory.

There is evidence that increased neural activity might compensate for ecstasy-related brain damage on low memory load tasks, and this might be responsible for the finding that ecstasy users and non-ecstasy-using controls display similar task performance on these low memory load tasks. Ecstasy users have shown greater parietal activity than non-ecstasy-using controls during low-load verbal n-back tasks in the absence of behavioral impairment during functional magnetic resonance imaging studies (Daumann et al., 2003a, Daumann et al., 2003b). Longitudinal follow-up found that continued ecstasy consumption was linked to further increases in parietal activity during low memory load tasks from the initial to the follow-up session 18 months later, again in the absence of behavioral impairment. The magnitude of the increased parietal activity was associated with a higher average nightly dose of ecstasy reported over the total period of ecstasy use (Daumann et al., 2004). Daumann et al. hypothesized that the additional cortical activity observed in ecstasy users might compensate for ecstasy-related brain damage, which would otherwise result in impaired performance. Increased cortical activity has also been found during a moderate memory load verbal short-term memory task in a number of brain regions including the medial superior gyrus, thalamus, and hippocampus in a sample of moderate LTEC ecstasy users (Moeller et al., 2004). Neither impaired behavioral performance nor altered cortical activity was found in ecstasy users on a verbal short-term memory task with low memory load (Jager et al., 2008), although these nonsignificant findings might be attributable to the low memory load of the task, which required that only a single stimulus be processed. In summary, ecstasy users showed increased cortical activity during short-term memory tasks with moderate memory load and during working memory tasks with low memory load, which is suggestive of a compensatory mechanism whereby increased cortical activity enables unimpaired behavioral performance despite ecstasy-related brain damage.

Studies examining cortical activity in ecstasy users have used functional magnetic resonance imagining, which measures the hemodynamic response related to neural activity in the brain. This method has low temporal resolution, and therefore, the cortical activity associated with specific cognitive processes occurring during working memory cannot be identified. Event-related potentials (ERPs), in contrast, have high temporal resolution, enabling examination of brain activity associated with specific memory-related processes occurring during task completion (Reinvang, 1999). ERPs would enable the altered patterns of cortical activity observed in ecstasy users to be linked to specific cognitive processes contributing to task completion.

Stimuli presented during working memory tasks typically elicit a parietally distributed positive ERP component identified as a P3b. The P3b component is thought to reflect the process of updating mental representations held in memory in response to incoming stimuli and ongoing task demands (Schmidt-Kassow et al., 2009). It has been proposed that P3b amplitude is reduced in more difficult tasks because cognitive resources are shifted away from the process of updating representations in memory and allocated towards other cognitive operations required by the task such as altering the order of presented stimuli (Garci-Larrea and Cezanne-Bert, 1998), updating retained stimuli (Segalowitz et al., 2001), or discriminating between stimuli (Polich and Criado, 2006). The P3b component elicited during a verbal working memory task, specifically a digits backward task, has been found to be smaller than that elicited during a verbal short-term memory task, specifically a digits forward task (Nulsen et al., 2010b, Fisk et al., 2011). It was hypothesized that during the verbal working memory task, cognitive resources were shifted away from updating representations in memory and toward the demanding task of retrieving the presented sequence in the reverse order (Nulsen et al., 2010b).

In the current study, ERPs elicited during verbal short-term and working memory tasks were examined to determine whether the electrophysiological activity occurring during task performance was affected by ecstasy consumption. Previous research has demonstrated that the P3b component is reduced in difficult tasks, particularly those that engage multiple processes such as working memory tasks. Ecstasy users show
impaired performance on working memory tasks, suggesting that these tasks are more difficult for ecstasy users to perform. Therefore, it is expected that the P3b component elicited during the more difficult working memory tasks will be reduced in ecstasy users to a greater degree than is observed in the non-ecstasy-using controls. This pattern of cortical activity would imply that ecstasy users employ more cognitive resources to perform the cognitive operations required by working memory tasks.

METHODS

Design

This study employed a mixed design with independent groups on the basis of history of drug use and repeated-measures factors of task type, as determined by sequence direction, for the behavioral tasks and task type and site for the electrophysiological data. Three participant groups were tested: those who had consumed ecstasy and other illicit drugs (ecstasy users), those who had consumed illicit drugs other than ecstasy (polydrug users), and those who had never consumed illicit drugs (non-users). The behavioral dependent variables were the span scores for the digits forward and digits backward tasks. The electrophysiological-dependent variables were the mean amplitudes of wave forms extracted from sites Fz, Cz, and Pz between 450 and 750 ms post-stimulus. This time window corresponded to that of the P3b component.

Participants

All participants had self-reported normal or corrected-to-normal vision and spoke English fluently. Four participants were excluded because of positive drug screens indicative of current intoxication or recent consumption of cannabis or meth/amphetamines. Four were excluded for failing to respond on more than 75% of trials, and two participants were excluded because of outlier scores, defined as standardized scores greater than 3.29, leaving 37 participants: 11 ecstasy users (four male), 13 polydrug users (four male), and 13 non-users (four male).

Materials

All participants completed a detailed questionnaire that requested demographic information and assessed alcohol, tobacco, and illicit drug use. The questionnaire also asked participants to provide the brand names of all ecstasy tablets they had taken or to describe the appearance of consumed pills. A saliva sample was collected from each participant and analyzed using the Cozart Drug Detection System SQ000381 (Siemens Ltd., Bayswater, Victoria, Australia) to detect the presence of tetrahydrocannabinol and meth/amphetamines. Premorbid intellectual functioning was assessed by administering the National Adult Reading Test (Nelson, 1991).

Software for the computer-administered recognition tasks was written in and presented with LabVIEW version 7.0 (National Instruments, Austin, Texas, USA). The electroencephalogram (EEG) was recorded with NuAmps and analyzed with Scan 4.3.

A 38-channel electrode cap (EasyCap (EASYCAP GmbH, Herrsching, Germany), Montage 40 excluding TP9 and TP10) with electrodes mounted according to the International 10/20 system was fitted prior to the computer tasks. Abralyt HiCL, a high chloride abrasive electrolyte gel, was used to ensure contact between the scalp and electrodes. Recordings were referred to the right mastoid, and AFz served as the ground. Vertical electrooculogram was recorded through electrodes above and below the left eye. Data were digitized at a sampling rate of 250 Hz and filtered online from DC to 70 Hz band-pass filter.

Procedure

Participants were requested to abstain from illicit drug use for seven days prior to the experimental session. Because of the sensitive nature of information requested in the drug and alcohol use questionnaire, verbal, rather than written, informed consent was obtained. Course credit or small financial remuneration was offered. This procedure was approved by the University of Western Australia Human Research Ethics Committee (RA/4/1/1430). All participants provided a saliva sample and completed the questionnaire. The experimenter was blind to the drug use status of participants.

The electrode cap was applied using standardized procedures. Participants were seated in a dimly lit, sound attenuating, shielded room, 90 cm from the computer screen. Participants completed the digits forward and digits backward serial recognition tasks with the order of presentation counterbalanced across participants.

Each trial began with a study phase during which sequences of between three and nine digits were randomly selected from the pool of digits 0–9 without replacement and presented in the center of the computer screen for 300 ms with inter-stimulus intervals of 700 ms. The digits were presented within a square frame subtending 2.06° visual angle. Each digit vertically subtended a visual angle of 1.37°. The conclusion of the display was signaled by a 100-ms tone. This was followed immediately by the test phase during which the sequence was re-presented. In the digits forward task, the test sequence was presented in the forward
direction, and in the digits backward task, the test sequence was presented in the backward direction. On half the trials in each task, the sequence of stimuli presented in the test phase was identical to that presented during the study phase, and on half the trials, the order of two temporally adjacent digits was reversed. The first of the two changed stimuli presented during the test phase is referred to as the first changed stimulus. Participants were required to indicate whether the test sequence matched or did not match the study sequence by pressing one of two response keys labeled ‘same’ or ‘different’. The next trial began immediately after the response or after 2 s had elapsed. Participants were administered six trials at each sequence length, totaling 42 trials. During sequence lengths greater than four when two temporally adjacent stimuli were switched, the two switched stimuli were constrained so that the changed stimulus did not occur as the first or last stimulus.

Data analysis

The brands of ecstasy pills participants reported consuming were searched for on www.pillreports.com, which is a website that provides an online forum for individuals to publish the results of chemical analysis of ecstasy pills. The published results for each brand of pills endorsed by ecstasy users were noted. The aim of this step was to exclude ecstasy users who reported consuming only ecstasy pills reported to contain chemicals other than 3,4-methylenedioxymethamphetamine (MDMA) or 3,4-methylenedioxymethamphetamine; no participants were eliminated. Kruskal–Wallis nonparametric analysis of variance was used to examine the frequency of reported drug consumption in the previous 12 months with Mann–Whitney U post hoc tests performed following significant values.

Span scores were calculated as the sum of the proportion of trials correct at each sequence length plus two. This scoring method has been described as a more sensitive measure of span than other methods, such as the longest sequence at which a proportion of trials are responded to correctly. Non-responses were coded as errors. Within-subjects 95% confidence intervals were calculated using Loftus and Masson’s (1994) technique. The spans obtained on each task were submitted to a mixed design analysis of variance (ANOVA) with direction (forward and backward) as the repeated-measures factor and group (ecstasy users, polydrug users, and non-users) as the between-subjects factor. The effect of reversal on performance was examined with paired sample t-tests comparing the forward and backward spans for each group.

Electrophysiological analysis

The EEG data were digitally filtered offline with a 0.05–30 Hz band-pass, zero phase-shift filter (12 dB down). An averaged mastoid reference was computed and replaced the right mastoid reference. Ocular artifact reduction was performed on the continuous EEG on the basis of eye blinks identified at the bipolar vertical electrooculogram channel. The regression-based subtraction procedure available in Scan 4.3 was employed to correct trials contaminated by eye blinks. Epochs encompassing an interval from 100 ms prior to the onset of stimuli and extending to 1000 ms post-stimulus were extracted at sites Fz, Cz, and Pz. Trials contaminated by artifact exceeding 150 μV were rejected. Averages were filtered with a 7 Hz low-pass zero phase-shift filter (12 dB down) for display purposes only.

The waveforms showed a parietally distributed positivity peaking at approximately 500–600 ms. On the basis of the visual inspection of the scalp topographies and latencies of the grand averages, this was labeled the P3b peak. The P3b amplitudes were quantified as the mean amplitude over an interval from 450 to 750 ms post-stimulus. The mean amplitude of the P3b component identified in the waveforms was submitted to ANOVA with site (Fz, Cz, and Pz) and direction (forward and backward) as repeated-measures factors and group (ecstasy users, polydrug users, and non-users) as the between-subjects factor. Greenhouse–Geisser corrections were used for data that violated sphericity as indicated by Mauchly’s test. Post hoc tests were performed following a significant F value using Fisher’s least significant difference (LSD). The magnitude of the effect of reversal on the P3b component was examined with paired sample t-tests comparing the mean amplitude of the P3b component elicited during the forward and backward tasks for each group.

RESULTS

Background variables

Demographic variables are reported in Table 1. Mean lifetime ecstasy consumption reported by the ecstasy-using group was 32.5 pills (SD = 27.2, range 7–80). Ecstasy users, polydrug users, and non-users were similar in age, years of education, and National Adult Reading Test scores.

Frequency of alcohol, nicotine, and illicit drug use during the previous 12 months is reported in Table 2. The groups varied in the frequency of other drug use reported over the previous 12 months (alcohol, nicotine, cannabis, speed (amphetamines), LSD, cocaine, and...
Table 1. Demographic characteristics and ecstasy consumption of ecstasy users, polydrug users, and non-users

<table>
<thead>
<tr>
<th></th>
<th>Ecstasy users (N=11)</th>
<th>Polydrug users (N=13)</th>
<th>Non-users (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.9 (2.6)</td>
<td>23.2 (3.3)</td>
<td>23.2 (4.5)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.1 (2.0)</td>
<td>15.9 (2.1)</td>
<td>16.1 (2.4)</td>
</tr>
<tr>
<td>Estimated lifetime consumption of cannabis, speed, cocaine, and prescription drugs</td>
<td>33.6 (4.4)</td>
<td>32.0 (5.3)</td>
<td>33.5 (4.8)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.1 (2.0)</td>
<td>15.9 (2.1)</td>
<td>16.1 (2.4)</td>
</tr>
<tr>
<td>Estimated lifetime consumption of ecstasy (number of pills)</td>
<td>32.5 (27.2)</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Duration of ecstasy use</td>
<td>4.0 (0.9)</td>
<td>4.0 (0.9)</td>
<td>4.0 (0.9)</td>
</tr>
<tr>
<td>Age first consumed ecstasy (years)</td>
<td>18.0 (2.2)</td>
<td>18.0 (2.2)</td>
<td>18.0 (2.2)</td>
</tr>
<tr>
<td>Time since last use</td>
<td>3.8 (1.7)</td>
<td>3.8 (1.7)</td>
<td>3.8 (1.7)</td>
</tr>
<tr>
<td>Average number of pills per session</td>
<td>1.2 (0.6)</td>
<td>1.2 (0.6)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>Maximum number of pills per session</td>
<td>2.9 (2.0)</td>
<td>2.9 (2.0)</td>
<td>2.9 (2.0)</td>
</tr>
</tbody>
</table>

*1 = 3 months; 2 = 6 months; 3 = 1 year; 4 = 3 years; 5 = 5 years; 6 = 7 years; 7 = over 7 years.
*1 = previous week; 2 = previous month; 3 = previous 3 months; 4 = previous 6 months; 5 = previous year; 6 = over a year ago.

Table 2. Frequency of use of alcohol and other drugs during the previous 12 months of individuals reporting drug use and time since last use

<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
<th>Percent reporting</th>
<th>Median time since last use (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecstasy users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>6 (2–6)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>2 (1–4)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>5 (2–6)</td>
<td>100</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>Speed</td>
<td>3 (1–5)</td>
<td>75</td>
<td>2.5 (1–5)</td>
</tr>
<tr>
<td>LSD</td>
<td>1 (1–2)</td>
<td>58</td>
<td>4 (4–6)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1 (1–4)</td>
<td>67</td>
<td>4 (2–5)</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>2 (1–5)</td>
<td>83</td>
<td>4 (2–6)</td>
</tr>
<tr>
<td>Polydrug users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>6 (3–6)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>1.5 (1–3)</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td>4 (3–5)</td>
<td>69</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>Speed</td>
<td>–</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>LSD</td>
<td>1 (1–1)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1 (1–2)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>1 (1–1)</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Non-users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>4 (1–6)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>1 (1–2)</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

Non-users reported no other drug use and hence are not shown in the table.
LSD, least significant difference.
*8 = daily; 7 = 4+ times per week; 6 = 2–3 times per week; 5 = 2+ times per month; 4 = monthly; 3 = every 2–3 months; 2 = 1–2 times per year; 1 = never.
*6 = daily; 5 = weekly; 4 = monthly; 3 = 3–4 times per week; 2 = 1–2 times per month; 1 = never.
*5 = >1 pack per day; 4 = 1 pack per day; 3 = 1 pack per week; 2 = 1 pack per month; 1 = none.
*1 = previous week; 2 = previous month; 3 = previous 3 months; 4 = previous 6 months; 5 = previous year; 6 = over a year ago.

Behavioral results

The mean span lengths, which are shown in Figure 1, were greater in the forward task than in the backward task ($F(1,34) = 39.83, p < 0.001$). The main effect of group was not significant ($F(2,34) = 0.735, p = 0.49$) nor did group membership interact with the effect of sequence direction ($F(2,34) = 1.19, p = 0.32$).

The average span obtained on the digits forward task was significantly higher than that obtained on the digits backward task in the ecstasy users ($t(10) = 6.20, p < 0.001$, Cohen’s $d = 1.71$), polydrug users ($t(12) = 2.30, p = 0.04$, Cohen’s $d = 0.69$), and non-users ($t(12) = 4.07, p = 0.002$, Cohen’s $d = 1.08$). Ecstasy users showed the greatest decrement in performance when required to respond to verbal stimuli presented in the backward direction indicated by the largest effect size. No significant relationships were found between measures of span and measures of ecstasy or other drug use. Regression analyses were conducted to determine whether LTEC or average number of ecstasy pills consumed per session predicted performance on the short-term or working memory task. LTEC did not significantly predict performance on the short-term memory task ($N = 11, \beta = -0.002$, $t(9) = -0.359$, ns) or on the working memory task ($N = 11, \beta = -0.004$, $t(9) = -0.432$, ns). The average number of ecstasy pills consumed per session also did not significantly predict performance on either prescription drugs). Ecstasy users and polydrug users reported more frequent alcohol consumption than non-users, and ecstasy users reported more frequent consumption of cannabis, speed, cocaine, and prescription drugs than polydrug users (all $p$s < 0.05).

Figure 1. Mean spans for non-users, polydrug users, and ecstasy users for each task with 95% within-subjects confidence intervals (DF, digits forward; DB, digits backward)
task (short-term memory task \((N=11, \beta = -0.419, t(9) = -1.557, \text{ns})\), working memory task \((N=11, \beta = -0.501, t(9) = -1.544, \text{ns})\)).

**Event-related potentials**

The grand averaged ERP wave forms elicited following the presentation of the first changed stimulus are presented in Figure 2.

The mean amplitudes of the waveforms elicited during the timing of the P3b component are shown in Table 3. There was a significant main effect of task direction on the mean amplitude of the P3b component \((F(1,34) = 24.31, p < 0.001, \text{partial } \eta^2 = 0.42)\). The P3b component was larger during the digits forward task \((M = 5.42, \text{SE} = 0.63)\) than the digits backward task \((M = 2.50, \text{SE} = 0.40)\). There was a significant main effect of site \((F(1,47, 49.93) = 36.96, p < 0.001, \text{partial } \eta^2 = 0.52)\) whereby the mean amplitude of the P3b component increased from anterior to posterior: the P3b component was smallest at frontal site Fz \((M = 2.22, \text{SE} = 0.51)\), larger at central site Cz \((M = 4.17, \text{SE} = 0.52)\), and largest at parietal site Pz \((M = 5.45, \text{SE} = 0.44)\). All post hoc comparisons between sites Fz, Cz, and Pz were significant (all \(ps < 0.05\)). There was a significant interaction between site and direction \((F(1.55, 52.88) = 5.58, p = 0.01, \text{partial } \eta^2 = 0.14)\). The mean amplitude of the P3b component was larger in the digits forward task than the digits backward task at site Fz (digits forward, \(M = 3.08, \text{SE} = 0.74\), digits backward, \(M = 1.35, \text{SE} = 0.56\)), at site Cz (digits forward, \(M = 5.66, \text{SE} = 0.73\), digits backward, \(M = 2.69, \text{SE} = 0.47\)), and at site Pz (digits forward, \(M = 7.52, \text{SE} = 0.67\), digits backward, \(M = 3.46\),

<table>
<thead>
<tr>
<th></th>
<th>Fz</th>
<th>Cz</th>
<th>Pz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecstasy users</td>
<td>Digits forward 2.02 (4.35)</td>
<td>4.80 (4.68)</td>
<td>7.42 (3.59)</td>
</tr>
<tr>
<td></td>
<td>Digits backward 1.91 (4.33)</td>
<td>3.49 (2.09)</td>
<td>4.82 (2.32)</td>
</tr>
<tr>
<td>Polydrug users</td>
<td>Digits forward 4.68 (5.34)</td>
<td>6.77 (4.54)</td>
<td>7.79 (4.76)</td>
</tr>
<tr>
<td></td>
<td>Digits backward 0.24 (2.82)</td>
<td>1.34 (2.81)</td>
<td>2.66 (2.32)</td>
</tr>
<tr>
<td>Non-users</td>
<td>Digits forward 2.54 (3.59)</td>
<td>5.39 (4.03)</td>
<td>7.34 (3.59)</td>
</tr>
<tr>
<td></td>
<td>Digits backward 1.91 (2.99)</td>
<td>3.25 (3.47)</td>
<td>2.90 (2.89)</td>
</tr>
</tbody>
</table>

Each mid-line site, Fz, Cz, and Pz.

Figure 2. Event-related potentials elicited to the first changed stimuli. The parietally distributed P3b (450–750 ms) is labeled. Forward tasks are shown in heavy line, and backward tasks are shown in fine line. The left hand panel shows ecstasy users’ grand averaged waveforms, the middle panel shows polydrug users’ grand averaged waveforms, and the right hand panel shows non-users’ grand averaged waveforms.

Group did not have a significant effect on P3b amplitude ($F(2,34) = 0.02, p = 0.98$, partial $\eta^2 = 0.001$) nor did it significantly interact with the effect of site ($F(4,68) = 0.76, p = 0.55$, partial $\eta^2 = 0.04$). There was a significant interaction between group and direction ($F(2,34) = 3.36, p = 0.05$, partial $\eta^2 = 0.16$). The mean amplitude of the P3b component was significantly larger in the digits forward task than in the digits backward task in the polydrug users (digits forward $M = 6.42, SE = 1.06$, digits backward $M = 1.41, SE = 0.69$) and in the non-users (digits forward $M = 5.09, SE = 1.06$, digits backward $M = 2.68, SE = 0.69$) (all $p s < 0.05$). In the ecstasy-using group, the mean amplitude of the P3b component elicited during the digits forward task ($M = 4.75, SE = 1.16$) was not significantly larger than that elicited during the digits backward task ($M = 3.41, SE = 0.75$) ($p > 0.05$).

At site Pz, the mean amplitude of the P3b component was significantly greater in the digits forward task than in the digits backward task in the non-users ($t(12) = 4.54, p = 0.001$, Cohen’s $d = 1.24$) and polydrug users ($t(12) = 4.53, p = 0.001$, Cohen’s $d = 1.08$) but not in the ecstasy users ($t(10) = 1.88, p = 0.09$, Cohen’s $d = 0.72$). A significant reduction in P3b amplitude was seen in polydrug users and non-users when responding to stimuli presented in the forward direction, but the reduction was not significant in the ecstasy-using group.

**DISCUSSION**

Ecstasy users, polydrug users, and non-users completed verbal short-term and working memory tasks while EEG was recorded to examine electrophysiological activity occurring during task performance. The ERPs elicited during task performance were expected to provide a more specific indication of the cognitive processes affected by ecstasy use. The results of this study suggest that the ecstasy-using group’s performance was negatively affected by the requirements of the working memory task to a greater degree than that of non-users or polydrug users, and this was reflected in the pattern of effect sizes found across the groups. Responding to stimuli presented in the reverse direction to that in the study phase reduced the ecstasy-using groups’ performance more than that of the non-users and polydrug users relative to performance when responding to stimuli presented in the forward direction. This supports the claim that ecstasy consumption impairs the ability to perform tasks requiring concurrent processing and retention of information, that is, working memory, relative to the ability to perform the same memory task without the concurrent processing requirement, that is, short-term memory. The findings from this study are consistent with those from Wareing et al. who found that ecstasy users demonstrated significantly impaired working memory performance that was not attributable to simple span limitations (Wareing et al., 2004a, Wareing et al., 2004b) and also fits with previous meta-analytic data that found that LTEC was related to working memory performance in ecstasy users but not short-term memory performance (Nulsen et al., 2010a). The current study also shows that ecstasy-related changes in working memory performance are present in low LTEC users and at moderate memory loads, where prior research had demonstrated this mainly in high LTEC users and at high memory loads.

The P3b component was significantly smaller in the digits backward task than in the digits forward task in the polydrug users and non-users, whereas this was not the case in the ecstasy users. The P3b component reflects the process of updating mental representations held in working memory, and the amplitude of the P3b component is indicative of the amount of cognitive resources allocated towards this process. When a second demanding process must be performed, such as retrieving mental representations of verbal stimuli in the reverse order, cognitive resources are shifted away from updating mental representations in working memory that results in a reduction in the amplitude of the P3b component (Garcia-Larrea and Cezañne-Bert, 1998, Polich and Criado, 2006; Nulsen et al., 2010b). One possible interpretation of the finding that P3b is reduced in the working memory task in non-users and polydrug users is that during this task, both groups allocated cognitive resources toward the demanding task of retrieving mental representations in the reverse order. This reduced the cognitive resources available for updating representations in working memory, leading to a reduced P3b component. The effect sizes suggest that ecstasy users did not show a significantly smaller P3b component in the working memory task than in the short-term memory task, which suggests that ecstasy users failed to allocate cognitive resources toward the task of retrieving the verbal stimuli in the reverse order to enable correct responding to the working memory.
task. Rather, cognitive resources remained focused on the process of updating representations in memory, and this distribution of cognitive resources was insufficient for accurate working memory performance.

Theoretical accounts of verbal working memory propose that sequences of verbal stimuli are retained in memory in the same direction as the initial presentation (Baddeley, 2000). When the sequence must be recalled in the reverse direction, the retained sequence is repeatedly covertly forward scanned to retrieve the appropriate stimulus. This is a strategic process that requires that cognitive resources be allocated between the task of updating representations in working memory and the task of covertly forward scanning the retained representations (Thomas et al., 2003). The results from the current study, specifically the smaller amplitude of the P3b during the working memory task than the short-term memory task, are consistent with previous findings (Valessi, Mappelli and Cherubini, 2009; Nulsen et al., 2010b) and support the proposition that verbal working memory engages multiple cognitive processes. The results from the current study also suggest that working memory performance is sensitive to changes in these cognitive processes when externally introduced variables, such as ecstasy consumption, negatively affect these individual cognitive processes.

Ecstasy-related changes in the allocation of cognitive resources may be the mechanism responsible for ecstasy-related impairments found in working memory and other cognitive complex tasks. Ecstasy users may have failed to engage the covert-forward scanning strategy during the digits backward task to the same degree as non-ecstasy-using controls. This failure impaired performance on the working memory task. Ecstasy users have shown impaired performance on other working memory tasks, which require that multiple processes be completed for accurate performance (Gouzoulis-Mayfrank et al., 2000) and also show impairments more clearly in cognitively complex tasks (Brown et al., 2010), which might reflect the failure of ecstasy users to appropriately allocate resources between the multiple cognitive processes needed to complete these tasks.

Limitations

The ecstasy users and polydrug users in the current study reported more frequent alcohol consumption over the previous 12 months, and this drinking behavior might have affected the electrophysiological activity recorded in each of these groups during the tasks. Chronic alcohol consumption has also been linked to impaired working memory and altered cortical function. Working memory function and related cortical activity were examined in a sample of binge drinkers (Crego et al., 2010). Binge drinkers showed unimpaired working memory performance. The binge drinking group also showed changes in the ERP components suggestive of reduced frontal activity.

The ecstasy-using group in the current study also reported more frequent use of cannabis over the previous 12 months than the polydrug users. The effect of cannabis and ecstasy/MDMA on neurotransmitters, body temperature, subjective mood, and hyperactivity have been known to interact, and it has been suggested that cannabis use may be a protective factor against the harmful effects of ecstasy consumption (Parrott et al., 2010). Hanson and Luciana (2010) found that lifetime cannabis consumption significantly predicted verbal memory function in a sample of polydrug users; however, their sample did not show impaired performance on measures of verbal memory function compared with nondrug-using controls. The authors concluded that ecstasy consumption therefore may not be the causal factor in apparent ecstasy-related memory impairments, and the impairments might be better classified as reflecting generally heavy drug use. Despite the difficulty in obtaining an ecstasy-using sample with limited exposure to cannabis, employing such a sample and comparing their working memory performance to that of non-users would provide a measure of ecstasy-related impairment unaffected by these interactions with cannabis.

The unknown chemical compounds in ecstasy tablets present a confounding factor when attributing ecstasy-related impairment to the action of specific chemicals. Pure ecstasy is MDMA; however, the purity of ecstasy tablets is variable and other chemicals such as caffeine or ketamine may be present (e.g., Yip and Lee, 2005). This confounding factor was addressed by requesting that all ecstasy users report the brand names of pills they had consumed. The aim of this was to exclude ecstasy users reporting consumption of only pill brands thought to contain chemicals other than MDMA or its close analogue 3,4-methylenedioxyamphetamine. This step did not lead to the exclusion of any participants. However, although the majority of ecstasy users were able to report a number of brands of pills they had consumed, comments on the questionnaires indicated that some users could not recall the brands of all of the pills they had taken. Attributing the results of the current study to the effects of MDMA can be done with greater confidence than if the suspected chemical contents of endorsed ecstasy brands had not been determined. This
step, however, does not completely eliminate this confound, and attributing the observed effects to MDMA must still be done cautiously.

The interaction between group and task did not reach conventional levels of statistical significance; however, planned comparisons and examination of the effect sizes indicate that reversal had a greater negative effect on ecstasy users’ performance than on non-ecstasy-using control’s performance. The power of the ANOVA to detect a significant interaction was diminished by the small sample size. The sample size was originally larger than was included in the ANOVA; however, individuals were excluded for testing positive for methamphetamines and cannabis, which reduced the sample size and the statistical power of the study.

The effects found in the behavioral data were consistent with those reported in previous research, notably that by Wareing et al. (2004a, 2004b), whereby ecstasy use appeared to impair working memory performance while leaving short-term memory performance relatively intact. The studies by Wareing et al. used larger sample sizes than the current study, which provide them with greater statistical power. These studies also used samples of ecstasy users with higher average LTEC than used in the current study. The findings from the meta-analysis conducted by Nulsen et al. (2010a) suggest that higher LTEC results in a greater decrement in ecstasy users’ working memory performance, and so, it stands to reason that studies using high LTEC samples have a large effect, which would be more likely to result in a significant group effect in an ANOVA. Studies with low LTEC samples, such as reported in the current thesis, are less likely to detect the smaller effect.

There was no relationship between measures of ecstasy consumption (LTEC, duration of use, average number of pills per session, and maximum number of pills in a single session) and the behavioral and electrophysiological measures. A significant relationship between these variables would enable the results to be more confidently attributed to the action of ecstasy rather than some other factors such as cannabis or alcohol consumption. Previous studies have reported significant correlations between measures of ecstasy consumption and verbal memory function (Fisk et al., 2009, Gouzoulis-Mayfrank et al., 2000), and as previously mentioned, the meta-analytic review conducted by Nulsen et al. (2010a) found a significant relationship between LTEC and the effect sizes associated with studies of ecstasy users’ working memory performance. However, the majority of studies do not report correlation or regression analyses of ecstasy consumption and cognitive performance, which may indicate a lack of significant finding. It might be that the relationship between ecstasy consumption and working memory performance is small and therefore only found when the range of ecstasy consumption is very wide, such as in the meta-analysis.

The ecstasy-using group reported more frequent use of illicit drugs in the previous 12 months than did the polydrug using group. Attributing the impairments observed in the ecstasy-using group to ecstasy use is confounded by the greater level of overall drug use reported by this particular group particularly LSD and cocaine. However, the pattern of behavioral results from this study concurs with a number of other previous studies that have matched ecstasy users and polydrug users on other drug use (Gouzoulis-Mayfrank et al., 2000, Reneman et al., 2001), and also concurs with those from a meta-analytic review of this literature (Nulsen et al., 2010a).

There was also a large discrepancy in the proportion of individuals reporting nicotine consumption in each of the participant groups; 100% of ecstasy users reported nicotine use, 69% of polydrug users, and 23% of non-users. There were no nicotine abstinence requirements prior to the study nor was the time since last cigarette recorded. Given that nicotine consumption and withdrawal can affect working memory performance (Sweet et al., 2010), it would be wise for future studies to control these variables.

CONCLUSIONS
Ecstasy users showed impaired verbal working memory performance, which might be due to ineffective allocation of cognitive resources between updating mental representations held in memory and the demanding task of processing stimuli within working memory. Ineffective allocation of cognitive resources might be the mechanism responsible for ecstasy users’ impaired performance on cognitively complex tasks such as working memory tasks. Sensitive measures of cognitive performance and cortical activity have found ecstasy-related changes, which, though subtle, might have serious and far reaching consequences.

CONFLICT OF INTEREST
No conflict of interest declared.

ACKNOWLEDGEMENTS
This study was supported by an Australian Postgraduate Award provided to C. Nulsen. Equipment costs were
supported in part by ARC grant DP0665616 to A. F. and a donation from the Local Drug Action Group of the University of Western Australia.

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