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Ecstasy-related deficits in the Updating Component of Executive processes

Running Head: Updating function in ecstasy users.

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Abstract

Aims: Research shows that users of ecstasy (MDMA) exhibit deficits in executive processes. The updating component appears to be particularly susceptible. Less is known about the precise nature of such deficits. The present study sought to determine if ecstasy-related deficits in memory updating are related to serial position of items presented, or length of the list of items. *Method:* Seventy-three ecstasy/polydrug users and seventy-three non-ecstasy users completed tasks of verbal and spatial memory running memory, recalling the most recent items, in lists of varying and unknown length. Participants were categorised according to letter and spatial span (4, 5, or 6), producing 6 sub-samples for analysis. *Results:* Ecstasy-polydrug users were impaired in 4 of the 6 sub-sample analyses. In three of these this was due to impaired recall of earlier serial positions. *Conclusions:* The results of the present study provide further support for updating deficits in ecstasy-polydrug users. The results are suggestive of a breakdown in the maintenance of information in working memory in terms of chunking; it appears that ecstasy/polydrug users are as able as nonusers to form memory "chunks" from the items, but that such chunks are not retained as effectively.

Introduction

In Cognitive Psychology, Baddeley's (1986) model of working memory consists of two "slave" systems- the phonological loop (for verbal processing and rehearsal) and the visuospatial sketchpad (for processing and rehearsing visual and spatial information), and a modality free central executive. More recently, Miyake and al (2000) have attempted to fractionate the central executive. They postulate that the central executive contributes to performance on a number of cognitive tasks through three main processes: moderating attention switching, inhibition of automatic responses and updating the contents of working memory. The updating component of the central executive requires monitoring and coding incoming information, assessing its relevance, and reviewing the contents of working memory. This involves deleting information that is no longer relevant, and replacing it with more recent salient information. The fundamental nature of memory updating is that it requires active manipulation of relevant information, rather than acting as a short-term store (Lehto, 1996; Miyake et al. 2000; Morris & Jones, 1990). Indeed to support this dissociation, neuroimaging studies show differences in activation between tasks requiring passive storage of information (parietal lobes) and those requiring the active manipulation of information (Dorsolateral Prefrontal Cortex- DLPFC) (Jonides & Smith, 1997). Moreover, as the usefulness of working memory as a whole is related to the efficiency with which we maintain, monitor, and edit the online contents, the updating component is one of the most often used functions in cognition (Carretti et al. 2005).

A number of studies have found that ecstasy users are impaired on tasks believed to tap the updating executive process. In the backward digit span task, participants listen to a string of digits and recite them to the experimenter in reverse order thus recruiting executive updating resources. Gouzoulis-Mayfrank et al. (2000)

found that ecstasy/cannabis users performed worse than nonuser controls on this task (although they were not impaired relative to cannabis only users, matched for cannabis use). In the same way as backward digit span, the subtracting serial sevens task (SSS) also recruits updating resources. Curran and co-workers have found ecstasy users make significantly fewer subtractions than nonusers on this task (Curran & Travill 1997; Curran & Verheyden 2003), while Morgan et al. (2002) found that ecstasy users made significantly more errors on the task.

Verdejo-Garcia et al. (2005) used a combined measure of updating (incorporating the backward digit span task, the arithmetic subtest from the WAIS-III, and the letter-number sequencing from the WAIS III) and found that ecstasy use was an important contributory factor in deficits in working memory updating among a clinical sample of poly-substance abusers. Indeed, severity of ecstasy use was the best predictor of performance on this dimension.

Research from our own laboratory has used indicators of memory updating similar to the operation span measure used by Miyake et al. (2000) in their influential study. For example, Wareing et al. (2004) used computation and reading span tasks, (analogous to Miyake et al's operation span task). Current ecstasy users were found to be impaired on the reading span measure (although the deficit was reduced to below statistical significance following inclusion of cannabis use as a covariate), and both current and previous ecstasy users were significantly impaired on the computation span task. Fisk et al. (2004) also used the computation span task and found that current ecstasy users attained a lower level than the nonusers. This remained significant after control for the use of other drugs indicating that memory updating performance is related to the use of ecstasy in this study.

In other research from our laboratory, we used the running letter memory task to assess updating performance. In this task participants are presented with a sequence of letters (the length of sequence being unknown to them). The task is to recall the last 'n' letters of the sequence. Thus as each new letter appears it is necessary to discard the first letter of the currently maintained set so as to incorporate the new letter. Our results revealed that ecstasy users recalled significantly fewer letters overall (Montgomery et al. 2005). However, in the version of the task we used, all individuals were required to recall the most recent six letters regardless of their letter span. It emerged that, at six letters, the maintenance element of the task exceeded the letter span of the majority of the participants that we tested. Consequently we could not rule out the possibility that many participants may have adopted a free recall recency based strategy negating the need for updating (Collette et al. 2006; Ruiz et al 2005; Smith-Spark et al. 2003). To address this possibility we repeated our original experiment (see Fisk & Montgomery in press) ensuring that the maintenance component of the task did not exceed the letter span of our participants. Thus each participant was asked to maintain a load that was equal to their letter span. We also included a visuo-spatial version of the task. Again in terms of overall performance we found ecstasy users to be impaired in both letter and visuo-spatial updating. However, while this study ensured that the maintenance element of the task was manageable, in order to produce scores for each participant that were comparable, we averaged performance over serial positions so that it was possible to compare the updating performance of individuals with different memory spans. In the event the ecstasy users on average had larger simple spans than nonusers effectively introducing this as a potential confound. Furthermore, the loss of the serial position data prevented us from exploring ecstasy user-nonuser group by serial position interactions and three way interactions between group, serial position and sequence length. Previous research has suggested that under conditions of updating, performance at the early serial positions is particularly disrupted. Equally while there is a drop in performance between the shortest sequence length and slightly longer sequences, thereafter performance levels off as list length increases (Fisk & Sharp, 2003; Morris & Jones, 1990; Smith-Spark et al 2007). Postle et al (2001) has described the three components processes involved in updating working memory. First unwanted material must be discarded; second the remaining material must be repositioned, and third new items must be added. It would be of value to further examine the exact nature of the ecstasy-related deficit in this task. If it is characterised by a more substantial drop in performance at the early serial positions then this might suggest that ecstasy users have problems with discarding and possibly repositioning; deficits at the middle serial positions might be consistent with a problem with repositioning or in the present context maintaining the temporal order information. Deficits at the final serial positions might suggest that users experience difficulty in encoding and adding new items. Alternatively, if there is no group by serial position interaction, it may the initial general drop in performance as list length increases is more pronounced in ecstasy users possibly implicating a more general resource constraint limitation.

In order to explore serial position and sequence length interactions with group, we matched users and non-ecstasy users on simply memory span. There were too few participants in our previous study (Fisk & Montgomery, in press) to produce sufficient numbers of users and nonusers with identical spans. For this reason we expanded our previous sample substantially. This allowed us to generate six sub-samples consisting of individuals with either spatial or letter spans of four, five, and six. Data for each of these sub-samples were analysed separately as indicated below.

Given the nature of ecstasy poly-drug use, it is possible that any observed deficits in cognitive functioning may be in part attributable to the concomitant use of "other" drugs (e.g. Croft et al. 2001). Indices of the frequency and intensity of other drug use will be collected and where possible, we shall attempt to evaluate the impact of these on the updating executive measures included in the present study.

To summarise, the purpose of the present study was to further explore the nature of updating executive process deficits in ecstasy users. In particular we sought to establish whether the ecstasy-related deficit was limited to specific serial positions or whether it was more general in nature but prevalent at only at specific sequence lengths. Measures of both letter and visuo-spatial updating were included and we collected data on the use of ecstasy and other illicit drugs.

METHOD

Design

Participants were categorised according to their verbal and spatial span scores. Thus separate analyses were conducted for those of span four, five, and six, and this was done separately for the verbal and spatial updating data. Thus six sub-samples were analysed. In each case, a mixed design was used with ecstasy user group (2 levels) as the between groups independent variable, and list length (number of items correctly recalled at lengths n, n + 2, n + 4, and n + 6; where n=span length) and serial position (with between four and six levels depending on span length) as the within participants independent variables. The dependent variable was the number of correct responses at the particular level and serial position (maximum six). For a response to be deemed correct both the spatial location (letter) and temporal order judgement had to be correct.

Statistical Analyses: Mixed ANOVA will be utilised. Group differences in serial position and sequence length effects and interactions between these will be explored though the use of orthogonal contrasts. For each independent variable, orthogonal contrasts compare performance at a particular level with performance averaged over some other subset of levels. Orthogonal contrasts are constructed so that each of these comparisons is independent in the sense that as a set they analyse wholly non-overlapping variance. Just as the main effects and interactions partition the total sum of squares in ANOVA allowing each effect to be evaluated, so orthogonal contrasts generate a further mutually exclusive partitioning. Effectively the degrees of freedom attributable to main effects or interactions are distributed among the set of contrasts so that each can be evaluated at conventional alpha levels without inflating the type 1 error rate. For example, it is possible to compare performance at the last serial position with performance averaged over all earlier serial positions. Furthermore we may explore whether this serial position effect is the same for different sequence lengths through utilising an interaction contrast. Finally, if the serial position effect differs between the two sequence lengths it is possible to further explore whether this difference is equivalent for users and nonusers (a three way interaction contrast).

Participants

Seventy-three ecstasy users (34 female) and 73 non-ecstasy user controls (57 female) completed the updating tasks. They included those tested in our previous study (Fisk & Montgomery, in press) as well as a substantial number of additional participants (an extra 19 users and 45 nonusers). Recruitment was via direct approach to university students, and the snowball technique (Solowij et al, 1992). Participants were requested to refrain from ecstasy use for at least 7 days prior to testing (the median period of abstinence was actually 4 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours prior to testing.

Materials

Patterns of drug use and other relevant lifestyle variables were investigated via means of a background questionnaire. The questionnaire gauged the use of ecstasy and other drugs, as well as current age, years of education, and other relevant lifestyle variables. In relation to illicit drugs, participants were asked a range of questions including frequency and duration of use and the last time that they had used each drug. Participants were also questioned concerning their history of drug use, and using a technique employed by Montgomery et al. (2005), these data were used by the experimenters to estimate total lifetime use for each drug. Average weekly dose and the amount of each drug consumed within the previous 10 days were also calculated.

Letter Span: Consonants were presented sequentially on a computer screen for 1.25 seconds. Participants were then required to recall the letters in the order in which they were presented. The task commences with three sets of two letters, and is then increased to three sets of three, four, five etc. (to a maximum of 10), until the individual fails on at least two out of three trials.

Spatial Span: This was analogous to the letter span task. A Corsi block type arrangement was presented on a computer screen and locations were highlighted for 1.25 seconds each. Participants were required to recall the locations in the order in which they were presented.

Letter Updating: This task was based on the running memory task (Morris and Jones, 1990). In this computer-based task, the participant was presented with a random sequence of consonants, based on their letter span score, on a computer screen. Twenty-four such lists were presented, and in each case, the participant was unaware of the number of consonants to be presented. The task was always to recall the most recent *n* consonants in the order in which they were presented (where *n* = the participant's letter span). The participant experienced six trials at each of the four list lengths: *n*, *n + 2*, *n + 4*, and *n + 6* items, and the order in which the lists were presented was randomised.

Spatial Updating: Again, this computer-based task was analogous to the letter updating task. Utilising a Corsi type arrangement, a random sequence of spatial locations was highlighted. Twenty four trials were presented in which the participant was unaware of the number of locations to be highlighted. The task was always to recall the most recent *n* locations in the order in which they were presented (where *n* = the participant's spatial span). The participant experienced six trials at each of the 4 list lengths: *n*, *n + 2*, *n + 4*, and *n + 6* items, and the order in which the lists were presented was randomised.

Raven's Progressive Matrices (Raven, Raven & Court, 1988): Each of the problems in Raven's Standard Progressive Matrices (SPM) was presented in the form of a sequence of symbolic figures. Participants were required to understand the nature of the relationships within each sequence and select one figure that completes each sequence. The Standard (SPM) consists of 60 problems divided into five sets of 12. In each set the first problem is self evident, the others becoming progressively more difficult. The test yields a total score out of 60 with a high score being indicative of good performance, and has been used extensively as an indicator of fluid intelligence.

The National Adult Reading Test (NART) (Nelson, 1982): The NART is an oral word reading test assessing premorbid intelligence. The test consists if 50 words of atypical phonology, whose pronunciations cannot be derived from standard grammatical rules (e.g. ache; gaoled). The total number correct was calculated for each participant, with a high score being indicative of high premorbid intelligence.

Procedure

Participants were informed of the general purpose of the experiment, and written informed consent was obtained. The tests were administered under laboratory conditions, and a computer running MS-DOS was used for the computer based tasks. The tests were administered in the following order (with order of updating tasks being alternated): background questionnaire, NART, letter span, spatial span, letter updating, spatial updating and Raven's progressive matrices. Participants were fully debriefed, paid £20 in store vouchers, and given drugs education leaflets. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

RESULTS

Background Variables.

Scores for background variables are set out in Table 1. The t test revealed that the ecstasy users did not differ significantly from the nonusers in terms of number of years of education, intelligence (Raven's and NART scores), spatial span, and cigarettes consumed. The ecstasy users did however report significantly higher average weekly alcohol consumption than nonusers, $t(138) = 3.23$, $p<.01$, were significantly older, $t(138.91) = 3.26$, $p<.01$ and had a significantly higher score on the letter span task, $t(144) = 2.28$, $p<.05$ (for age Levene's test was significant so degrees of freedom have been adjusted accordingly). Gender distribution was also significantly different between the groups, with females accounting for 47% of ecstasy users and 78% of non ecstasy users, χ^2 (df. 1, N=146) = 15.43, p<.001.

<<Insert Table 1 about here>>

Indices of Drug use

It is clear from inspection of Table 2 that while the ecstasy users were also regular users of other drugs, in the nonuser group this was restricted mainly to the use of cannabis. The ecstasy users smoked cannabis significantly more often than nonusers (2.40 times a week compared to 0.47), t(79.97) = 5.10, p<.01; had a higher total lifetime dose (2646 joints compared to 238 joints) t(58.65) = 4.45, p<.01; and had a higher average weekly dose (8 compared to 2 joints) t(66.08) = 3.93, p<.01. In all cases, Levene's test was significant so degrees of freedom have been adjusted accordingly. While all of the users in the present study consumed ecstasy, it is clear that the level of consumption of other drugs is such that the individuals concerned might be better described as ecstasy/polydrug users.

<<Insert Table 2 about here>>

Updating Performance

As noted above, separate analyses were conducted according to the participant's span length (span = 4, 5, or 6). Thus six separate analyses were conducted, three for letter and three for spatial span. Inspection of Figures 1 and 2 reveals that the trends observed were as expected. For both spatial and letter updating performance steadily declines as participants attempt to recall stimuli at progressively earlier serial positions[1]. Also again for both letter and spatial updating, with one exception, performance declines for sequences of span-plus-2 relative to sequences equal to the participant's span. For the longer sequences the mean number of correct responses remains depressed, but there is no further consistent decline in performance as sequence length increases[2]. Since it is known that ecstasy/polydrug users are impaired on these tasks, the purpose of the present paper is to explore the basis of the deficit. The remaining analyses seek to establish whether the ecstasy/polydrug deficit is more apparent at specific serial positions or whether the sequence length effect noted above is more pronounced in ecstasy/polydrug users. The possibility of statistically significant three way interactions will also be explored.

<<Insert Figures 1 and 2 about here.>>

Mean number of correct responses (maximum 6) and corresponding standard deviations for individuals[3] with simple span scores of four, five, or six for both spatial and letter updating are set out in Tables 3 and 4. The Tables also reveal for each span length how many participants were included in the sub-sample. Data are disaggregated by sequence length (span, span + 2, span + 4, and span + 6) and by serial position (ranging from serial positions 1 to 4, to positions 1 to 6 according to span length). Averaged over sequence length and serial position, it is clear that compared to nonusers ecstasy/polydrug users achieved lower scores in all but one case (see the bottom rows in Tables 3 and 4). However inspection of Table 5 reveals that on a two tailed basis, the overall group difference was only statistically significant in one of the six analyses (letter updating performance for those individuals with a simple span of 5). Nonetheless the difference approached statistical significance with the letter updating sample (with a simple span of 6) and the spatial updating sample (with a simple span of 5) and since the prediction was directional (i.e., that ecstasy users would perform worse), on a one tailed basis these group differences are also statistically significant.

<<Insert Tables 3, 4, and 5 about here>>

Further inspection of Table 5 reveals that several two-way interaction contrasts were statistically significant or approached significance. For example, in relation to the sample with spatial span equal to four, there was a serial position (position 1 versus position 2) by Group interaction, p=.029. This was because the ecstasy/polydrug related deficit was more evident in the recall of serial position 1 stimuli relative to the serial position 2 outcome.

Those with a spatial span equal to five produced a number of two-way interaction contrasts that achieved or approached significance. The length by group interaction approached significance, p=.071. This was because the ecstasy/polydrug user related deficit was evident for sequences equal to the participants' span but less evident when averaged over sequences of longer length (p=.081). Similarly the user-related deficit evident for sequences of span plus 2 contrasts with the virtual absence of a deficit for longer sequences (p=.040). In common with the results reported above for the spatial span 4 sample, participants with a spatial span of 5 also demonstrated a serial position by group interaction contrast although in this case it only approached significance (p=.074). This was because the ecstasy/polydrug user-related deficit evident for recall at serial position 1 was of a larger magnitude than that evident for serial position 2.

The spatial updating analyses (Table 5) also revealed several complex statistically significant three-way interaction contrasts. A two-way interaction addresses the issue of whether the profiles connecting the cell means deviate from parallelism. In the present context, a three-way interaction essentially evaluates whether any deviation from parallelism is the same for both groups. In all cases the significant three-way contrasts expand upon the serial position effects noted above. Specifically they reveal that the ecstasy/polydrug deficits that are apparent at the early serial positions are not evident at all sequence lengths. For example, participants with a spatial span of 4 generated responses which produced a statistically significant three-way interaction (p=.05). This was qualified by two statistically significant three-way interaction contrasts. The first (see Figure 3) reveals that the ecstasy/polydrug deficit evident at the early serial positions is significantly larger for sequences of length 6 compared to the situation for the longer sequences, p=.005. However, the second contrast (displayed in Figure 4) reveals that the early serial position deficit is not uniform at the longest sequence lengths being significantly larger for sequences of length 10 compared to sequences of length 8, (p=.048).

<<Insert Figures 3 and 4 about here>>

For the sample with a spatial span of five, one three-way interaction contrast approached significance. Examination of Figure 5 reveals that the ecstasy/polydrug deficit averaged over the first four serial positions was significantly greater for the shortest sequence (of length 5) compared with the situation prevailing over the longer sequences (p=.055).

<<Insert Figure 5 about here>>

In relation to the letter updating task none of the two way interactions were statistically significant nor did any approach significance. For participants with a letter span of six, two of the three-way interaction contrasts were statistically significant. As with the spatial updating task, ecstasy/polydrug users exhibited deficits in recall of the early serial positions. However this was not apparent at all sequence lengths. Specifically inspection of Figure 6 reveals that the early serial position deficit was more evident for sequences of length 8 relative to longer sequences (p=.029). Furthermore, examination of Figure 7 reveals that at sequence length 10 the ecstasy/polydrug deficit is larger at serial position 2 relative to the deficit at serial position 1, while for sequence length 12 the opposite pattern emerges with the deficit virtually absent at serial position 2 while substantially larger at serial position 1 (p=.011).

<<Insert Figures 6 and 7 about here>>

Correlations with Indices of Drug Use.

Given the extent of polydrug use among the ecstasy-using sample (see Table 2), it is possible that some or all of the ecstasy-related effects might have been attributable to other drugs. The fact that the present sample was disaggregated according to span length meant that there were relatively few cannabis users among each of the sub-samples. This, together with the small number of cocaine users among the non-ecstasy group, rendered the use of ANCOVA inappropriate since it would not be possible to properly test for homogeneity of regression. To assess the possible role that other drugs may have played in accounting for the present results we resorted to correlational analyses. Various measures of recent and long-term use of ecstasy, cannabis, and cocaine were correlated with the aggregated[4] letter and spatial updating scores. The results are set out in Table 6. None of the indicators of cocaine or cannabis use were significantly correlated with letter and spatial updating. Total lifetime use and average weekly dose of ecstasy were significantly correlated with both letter and spatial updating performance. The correlations were negative indicating that higher levels of ecstasy use were associated with poorer updating performance. Recent consumption of ecstasy (during the previous 10 days) and current frequency of use were both significantly and negatively associated with spatial updating performance. The correlation between the frequency of ecstasy use and letter updating was just short of statistical significance, p=.052. With regard to alcohol and tobacco, neither the number of cigarettes smoked per day nor the units of alcohol consumed per week were significantly correlated with spatial and letter updating performance. Indeed the correlations were for the most part near to zero[5].

<<Insert Table 6 about here>>

DISCUSSION

Ecstasy/polydrug users were impaired in four of the six sub-samples that were analysed. In three of these cases (for the spatial span 4 and 5 and letter span 6 sub-samples) the deficit was characterised by impairment in recall of stimuli at the early serial positions. However, this impairment was not evident at all sequence lengths. There was a tendency for the deficit to be less evident at the longer sequence lengths where the performance of both groups was substantially reduced. Participants with a letter span of 5 showed an overall ecstasy/polydrug related deficit but in this case there were no group by serial position or group by sequence length interactions. Two sub-samples showed no ecstasy/polydrug related effects. However in both cases one or both groups had relatively few participants. Specifically there were only 13 users with a letter span of four and only nine nonusers with a spatial span of six. Thus with limited statistical power to detect a significant group difference, there is a heightened risk of a Type 2 error here.

In so far as we have established ecstasy/polydrug related deficits in both spatial and letter updating performance, the present results are the same as those previously obtained by our laboratory (Fisk & Montgomery in press). This is not surprising since the samples were overlapping in that the data for those who took part in our previous study have been included here. The present sample was augmented further so as to allow the investigation of different sub-samples with varying simple span lengths. However, as noted above, in an earlier study from our laboratory in which a different group of participants were asked to recall the last six letters in sequences of varying (unknown) length, an ecstasy related deficit was also observed (Montgomery et al. 2005).

How might we account for the finding that the ecstasy/polydrug deficit appears more likely to manifest itself at the early serial positions? As noted above Postle et al (2001) has identified three subcomponent processes involved in the updating task. The first of these involves discarding unwanted letters at the beginning of the current set and the second involves repositioning the remaining items while maintaining their temporal order. The ecstasy/polydrug deficit evident in the recall of the early serial positions might suggest that users are specifically impaired in one or both of these sub-processes. In the two substantive spatial updating analyses deficits were especially evident in the first serial position, which would implicate the first process (discarding). However, although the same trend was evident in one of the letter updating analyses (for participants of span 6) it did not produce a straightforward early serial position by group interaction.

An additional factor identified by Postle et al (2001) as influencing performance on the letter updating task was 'group integrity'. This reflects the extent to which the formation of chunks might affect updating performance. By presenting the letter sequences in chunks of differing lengths, it was possible to compare performance in contexts where the updating process did not result in the break up of chunks with other situations in which discarding the earliest serial position modified the chunk containing it. Postle et al. found that breaching group integrity in this manner compromised performance. Such disruption invariably occurs in the early serial positions. While the present study did not present stimuli in chunks it seems likely that participants constructed their own chunks during the encoding process.

Indeed Postle et al. maintain that group context is encoded automatically in working memory stimulus representations. In the context of visuo-spatial serial recall it is clear that participants do form chunks although it is unclear whether these chunks or clusters might be formed on the basis of spatial proximity (De Lillo, 2004) or temporal contiguity (Parmentier et al. 2006). Participants have also been observed to form chunks when processing digits strings of varying length (Fendrich & Arengo, 2004) and it seems reasonable to assume that a similar strategy might be employed when processing letter sequences. Thus the deficits in the processing of the early serial positions in updating tasks may be a consequence of the destruction of chunks, which are formed naturally and automatically during the encoding process. It may be that ecstasy/polydrug users are especially susceptible to this effect. The fact that simple serial recall is unimpaired in ecstasy/polydrug users suggests that they have no problem in forming the chunks but that the disruption caused by the updating process results in more elements of the disrupted chunk being lost.

Aside from the issue of ecstasy/polydrug related deficits the present results suggest that updating is an all or nothing process and does not involve a cumulative increase in cognitive demands as list length increases. Research in other populations suggests that in running memory tasks, there is little evidence of a cumulative effect of list length i.e. updating, once activated, will place continuous strain on executive resources regardless of list length (e.g. Fisk and Sharp 2003). Fisk and Sharp also suggest that it is possible that each successive update in a running memory task may be done in an “on-off” manner, which may generate a uniform demand on the executive system, rather than increasing demands with increasing list length. Similar findings have been reported by Postle et al. (2001) and Morris and Jones (1990).

The results also provide further evidence for the possible localisation of ecstasy-related degradation (whether this be temporary or permanent). Salmon et al. (1996) used a letter-updating task adapted from Morris and Jones (1990) requiring participants to recall the most recent six items from strings of eight, nine and ten consonants. Brain activation during the updating task was compared to that during a phonological short-term memory task. For the updating task only, an increase in activation was seen in the mid-dorsal prefrontal cortex (DLPFC), i.e., BA 9, the left middle frontal regions (BA 46 and BA 10) and in the right frontal pole (BA 10). In a more recent study using PET imaging, Van der Linden et al. (1999) required participants to remember the most recent 4 items in letter strings of varying length and it was found that the most significant increases in activation occurred in the left frontopolar cortex (BA 10) spreading to the left middle frontal area (BA 46). Utilising ERP and neural imaging techniques, Postle and co-workers provide further support for the role of the dorsolateral prefrontal cortex in updating tasks (e.g., Postle et al. 2001). Most recently, utilising PET, Collette et al (2005) obtained similar results observing that tasks believed to recruit the updating executive process, while each activating unique cortical areas, shared in common activation of the DLPFC (including the frontopolar cortex BA10 as well as BA 6 BA 9 and BA 46), the VLPFC (BA 44 and BA 45) and the orbitofrontal cortex (BA 11). Interestingly interaction analyses revealed that it was specifically the left frontopolar gyrus (BA 10) that is associated more specifically with updating than with the other executive functions. The fact that ecstasy users appear to exhibit deficits on a <u>variety</u> of updating tasks and not in tasks which involve the switching or inhibition executive processes (Montgomery et al. 2005) suggests that the cortical areas potentially responsible are most likely not task specific but reflect areas supporting functions common to many updating tasks and which do not feature in switching or inhibition, specifically the frontopolar cortex (BA 10). If MDMA-related neurotoxicity is responsible for the deficits that have been observed it is not clear whether neuronal degradation is more extensive in the frontopolar cortex or whether this area is more sensitive to the effects the axonal damage and serotonergic down regulation which is believed to occur as a consequence of MDMA use (see Morgan 2000 for a review of the neurotoxic potential of MDMA in humans and animals).

While it was not possible to control for the effects of other drugs through the use of ANCOVA, the results obtained here suggest that it is aspects of ecstasy use that are significantly associated with updating performance rather than the use of other illicit drugs. Indeed none of the correlations between different aspects of cocaine and cannabis use and updating performance were statistically significant.

While the results of the present study are consistent with those obtained previously in our laboratory it must be conceded that not all studies have found ecstasy users to be impaired on tests believed to tap the updating executive component process. While ecstasy-related deficits have occasionally been found on the backward digit span task they have not always been observed (Bhattachary & Powell 2001; Gouzoulis-Mayfrank et al. 2003; McCardle et al. 2004; Thomasius et al. 2003) and while deficits may be initially present they sometimes disappear following statistical controls for the use of other drugs (e.g., Reay et al 2006). Also there appears to be little ecstasy-related impairment in the n-back task (Daumann et al. 2003; Gouzoulis-Mayfrank et al. 2003; Jacobsen et al. 2004). Using a similar task (the Tic-Tac-Toe task), Alting von Geusau et al. (2004) found that users were unimpaired (although in male users there was a significant interaction indicating that they performed worse under high demand conditions). It remains unclear why deficits are not consistently found. It may be that tasks requiring information to be continuously discarded from working memory and which carry a substantial serial recall component, as is the case with letter and spatial updating and computation span, are especially susceptible.

As with most studies in this area, there are a number of limitations. Due to the quasi-experimental design of the study, it remains possible that the groups differed on some variable other than ecstasy use. Some possibilities have been excluded such as intelligence (NART and Raven's). Gender was also significantly different between the groups, although we have no reason to believe that gender would be an important contributory factor to updating performance. However, possible group differences in other aspects affecting performance such as general health, nutrition, or some premorbid condition predating drug use (Verheul, 2001) cannot be ruled out.

As with the majority of retrospective studies in this area, we cannot guarantee the purity of the tablets consumed by the ecstasy users (Cole et al 2002). Though in a recent review of the literature, Parrott (2004) reports that analysis of the contents of ecstasy tablets from amnesty bins in nightclubs revealed that purity of tablets is approaching 100% MDMA. Due to limited resources we were also unable to objectively measure drug abstinence (e.g. from hair or urine samples). This is not uncommon with research in this area, and most published studies do not report such measures (e.g. Fox et al. 2002; Heffernan et al. 2001; Morgan 1998; Morgan 1999; Rodgers 2000).

The focus of the present paper was the nature of updating deficits in ecstasy polydrug users. However, as mentioned earlier, other executive functions may also be susceptible to the effects of illicit drugs. Switching and inhibition have also been investigated in ecstasy users. For example Fox et al. (2002) found increased latencies where switching attention was required. Similar to updating, there is likely to be subprocesses involved in switching performance (e.g. the disengagement of an irrelevant task set, and the engagement of another). Accordingly future research should seek to investigate the nature of switching and inhibition process in ecstasy users.

In conclusion, the results of the present study provide further support for an ecstasy-related deficit in memory updating that is not obviously related to the use of other recreational drugs. Outside the area of psychopharmacology, it also provides further support for the nature of the updating process, suggesting that updating the contents of working memory in a running memory task may be a non cumulative all or nothing process with each update placing an equivalent load on executive resources. Furthermore it is possible that the process undermines the group integrity of naturally occurring chunks that are produced during the encoding phase thereby impairing recall of the early serial positions under updating conditions.

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Table 1: Age, Years of Education, Intelligence, Span Scores, Cigarette and Alcohol Consumption for Ecstasy Users and Nonusers.

	Ecstasy users		Nonusers		Sig
	Mean	S.D.	Mean	S.D.	
Age (years)	21.77	2.11	20.73	1.73	p<.01
Years of Education	15.60	2.08	15.78	1.47	
Raven's Progressive Matrices (Max. 60)	46.97	6.03	48.55	5.37	
NART (Max. 50)	27.85	5.94	27.99	5.03	
Spatial Span	4.74	0.85	4.50	0.80	
Letter Span Score	5.23	0.74	4.96	0.72	p<.01
Units of Alcohol (per week)1	21.17	12.68	14.66	11.40	p<.01
Number of Cigarettes (per day)2	9.50	7.21	6.53	3.76	

1. Five non ecstasy users indicated that they did not consume alcohol. These five were not included in the estimation of the mean and standard deviation.
2. Forty ecstasy users and fifteen non ecstasy users were currently smoking. Only these persons were included when calculating the mean and standard deviation.

Table 2: Indicators of Drug Use Among Ecstasy Users and Non Ecstasy Users

	Ecstasy Users				Non Ecstasy Users			
	Mean	Median	S.D.	n	Mean	Median	S.D.	n
Frequency of Use (times per week)[1]								
Ecstasy	0.32	0.25	0.43	73	-	-	-	-
Cannabis	2.40	1.13	2.56	56	0.47	0.06	0.97	26
Cocaine	0.58	0.25	1.43	26	0.63	0.63	0.53	2
Amount Used During Previous 10 Days[2]								
Ecstasy (tablets)	3.46	2.00	4.23	13	-	-	-	-
Cannabis (joints)	7.77	2.50	10.09	29	5.67	2.50	6.19	6
Cocaine (grams)	0.44	0.30	0.36	13	2.00	2.00	-	1
Total Use[3]								
Ecstasy (Tablets)	309.86	169.00	486.25	73	-	-	-	-
Cannabis (joints)	2645.55	559.00	3985.85	56	237.60	26.00	481.01	26
Cocaine (grams)	52.46	27.00	83.11	26	159.00	159.00	216.37	2
Average Weekly Dose[3]								
Ecstasy (tablets)	1.63	1.10	1.66	72	-	-	-	-
Cannabis (joints)	7.76	3.73	10.71	53	1.57	0.19	2.78	24
Cocaine (grams)	0.29	0.16	0.35	25	0.65	0.65	0.50	2
Weeks since last use								
Ecstasy	32.15	4.00	62.82	73	-	-	-	-
Cannabis	34.93	0.50	94.20	60	54.09	8.00	111.43	38
Cocaine	17.85	3.00	45.16	57	51.76	10.00	82.30	6

Notes:

1. Regular users only. Refers to frequency over lifetime use.
2. Refers only to individuals who have consumed the drug in question during the previous 10 days.
3. Some participants, including occasional or single use individuals were unable to quantify their previous use.

Table 3 Spatial Updating Performance for Ecstasy/Polydrug Users and Nonusers for Participants with Simple Spans ranging from Four to Six

Sequence Length		Four				Five				Six			
	Serial Position	User (n=26)		Nonuser (n=35)		User (n=28)		Nonuser (n=23)		User (n=15)		Nonuser (n=9)	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Span	1	4.27[a]	1.37	4.40	1.24	3.61[a]	1.47	4.57	1.38	2.60	1.64	3.56	1.33
	2	4.19	1.39	4.37	1.46	2.50[b]	1.26	3.52	1.08	2.73	1.62	2.89	1.05
	3	4.73	1.00	4.97	1.29	3.86	1.15	4.35	1.19	2.93	1.62	2.67	2.00
	4	5.23	0.71	5.09	0.95	4.32	1.63	4.70	0.97	3.87	1.41	3.11	1.76
	5					4.89	1.23	5.13	0.97	4.93	1.22	4.44	1.42
	6									5.53	0.83	5.33	0.87
Span + two	1	2.08	1.32	3.17	1.44	1.50[c]	1.43	2.22	1.35	1.47	1.55	1.78	0.83
	2	3.31[c]	1.12	3.89	1.37	2.21	1.29	2.57	0.90	2.40	1.59	2.00	1.50
	3	4.62	1.10	4.91	1.12	3.11	1.73	3.57	1.34	2.87	1.68	2.33	1.80
	4	5.15	1.01	5.03	1.20	4.32	1.61	4.74	1.18	4.20	1.47	3.78	1.30
	5					5.04[a]	1.00	5.61	0.58	4.67	1.11	4.67	1.41
	6									4.93	1.28	5.56	0.73
Span + four	1	2.88	1.03	3.09	1.42	2.46	1.07	2.83	1.47	1.33	0.98	1.56	1.24
	2	3.50	1.33	3.43	1.40	2.93	1.33	2.74	1.79	2.40	1.35	2.44	1.67
	3	4.65	0.98	4.97	0.95	3.61	1.17	3.35	1.47	3.40	1.45	3.78	1.30
	4	5.15	0.92	5.23	1.09	4.57	1.10	4.52	0.99	3.93	1.10	4.11	0.78
	5					5.21	0.79	5.30	0.82	5.20	0.94	5.22	0.97
	6									5.53[c]	0.74	6.00	0.00
Span + six	1	2.73[c]	1.54	3.37	1.37	1.71	1.44	1.87	1.14	1.27	1.16	1.89	1.05
	2	3.69	1.46	3.71	1.53	2.68	1.22	2.30	1.02	2.20	1.46	2.22	1.48
	3	4.73	1.12	4.54	1.24	3.79	1.45	3.65	1.27	2.93	1.58	3.78	1.64
	4	4.85[c]	1.19	5.29	0.83	4.61	1.20	4.96	0.98	4.20	1.37	4.78	1.20
	5					4.89	1.55	5.30	0.76	4.80[c]	1.21	5.56	0.53
	6									5.33	0.96	5.89	0.33
Total		4.11	0.65	4.34	0.74	3.59	0.68	3.89	0.43	3.56	0.71	3.72	0.57

Table 4 Letter Updating Performance for Ecstasy/Polydrug Users and Nonusers for Participants with Simple Spans ranging from Four to Six

Sequence Length		Four				Five				Six			
Serial Position		User (n=13)		Nonuser (n=19)		User (n=30)		Nonuser (n=36)		User (n=30)		Nonuser (n=17)	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Span	1	5.31	1.32	5.68	0.48	4.40	1.50	4.56	1.44	4.40	1.77	5.06	1.14
	2	5.08	1.12	5.00	1.05	4.07	1.60	4.50	1.40	4.07 [c]	1.60	4.82	1.13
	3	5.23	1.17	5.32	0.89	3.90	1.60	3.97	1.16	4.33	1.35	4.94	1.25
	4	5.62	0.65	5.53	0.77	4.60	1.33	4.78	1.05	4.23	1.19	4.47	0.80
	5					4.97	0.85	5.03	0.88	4.83	1.18	5.12	0.86
	6									5.03	0.89	5.24	0.75
Span + two	1	1.85	2.23	2.37	2.17	1.53	1.22	1.81	1.06	1.80	1.73	2.65	1.80
	2	3.92	1.89	4.05	1.35	2.03	1.35	2.31	1.21	2.70 [a]	1.74	3.71	1.49
	3	5.38	0.87	5.21	1.13	3.57 [a]	1.57	4.25	1.13	3.20	1.63	3.88	1.41
	4	5.85 [c]	0.38	5.32	1.00	4.43 [c]	1.25	4.94	1.12	4.40	1.16	4.82	1.01
	5					4.87 [c]	1.31	5.36	0.72	5.10	0.92	5.06	1.09
	6									5.13	0.97	5.41	0.87
Span + four	1	3.38	1.19	3.47	1.61	1.07 [a]	1.17	1.78	1.29	1.47	1.22	2.06	1.52
	2	4.08	1.26	4.05	1.51	2.33 [a]	1.30	3.00	1.10	1.83 [a]	1.37	2.71	1.31
	3	4.77	1.17	5.05	0.78	3.70 [a]	1.32	4.39	1.08	3.67	1.54	3.35	1.62
	4	5.62	0.65	5.37	0.76	4.30 [c]	1.37	4.78	0.96	4.20	1.24	4.12	1.36
	5					5.17	0.87	5.39	0.84	4.87	1.14	5.00	0.79
	6									5.40	1.00	5.41	0.87
Span + six	1	2.08	1.38	2.63	1.95	1.27	1.05	1.61	1.23	1.63	1.52	2.24	1.79
	2	3.69	1.32	3.37	1.54	2.03	1.45	2.56	1.25	2.33	1.58	2.29	1.61
	3	5.00	1.08	4.68	1.38	3.23	1.59	3.39	1.50	3.50	1.72	3.53	1.94
	4	5.77	0.44	5.47	0.90	4.20 [c]	1.67	4.81	1.09	3.67	1.56	4.18	1.63
	5					4.97 [c]	1.07	5.39	0.73	4.90	1.21	5.41	1.28
	6									5.30	0.88	5.65	0.79
Total		4.54	0.70	4.54	0.77	3.53	0.72	3.93	0.43	3.83	0.77	4.21	0.67

[a] Difference significant at $p<.05$
[b] Difference significant at $p<.01$
[c] Difference significant at $p<.05$ (one-tailed)

Table 5. F values from the Spatial and Letter Updating Analyses for the Main Effect of Group and Interaction contrast Effects including Group

Task/Span	Main effect of group	Two way interactions with Group	Three way interactions with group
Spatial 4	F(1,59)=1.60, p=.211	1. Length by Group F(3,177) = 0.84, p=.472 2. Serial by Group F(1.81,106.54)= 1.81, p=.173 **3. Serial (pos 1 vs 2) by group F(1,59) = 5.00, p=.029**	**1. Length by Serial by Group F(6.71,395.78)=2.06, p=.05** **2. Length (span+2 vs span+4&+6) by Serial (pos 4 vs pos3&2&1) by Group F(1,59)=8.35, p=.005** 3. **Length (span+4 vs span+6) by Serial (pos 3 vs pos2&1) by Group F(1,59)=4.09, p=.048**
5	F(1,49)=3.31, p=.075	1. Length by Group F(3,147) = 2.39, p=..071 2. Serial by Group F(3.23,158.19) = 1.17, p=.324 3. Serial (pos 1 vs 2) by group F(1,49) = 3.34, p=.074 4. Length (span vs span+2&+4&+6) by Group F(1,49)=3.18, p=.081 5. **Length (span+2 vs span+4&+6) by Group F(1,49)=4.43, p=.040**	1. Length by Serial by Group F(7.92,387.99)=0.85, p=.560 2. Length (span vs span+2&+4&+6) by Serial (pos 5 vs pos4&3&2&1) by Group F(1,49)=3.87, p=.055
6	F(1,22)=0.33, p=.569	1. Length by Group F(3,66) = 1.36, p=..260 2. Serial by Group F(3.38,74.36)= 0.86, p=.477	1. Length by Serial by Group F(7.89,173.47)=0.77, p=.631
Letter 4	F(1,30)=0.00, p=.993	1. Length by Group F(3,90) =0.08, p=..971 2. Serial by Group F(1.93,57.95) = 1.60, p=.211	1. Length by Serial by Group F(6.02,180.67)=0.62, p=.713
5	**F(1,64)=7.68, p=.007**	1. Length by Group F(3,192) =0.82, p=..485 2. Serial by Group F(2.65,169.56) = 0.22, p=.863	1. Length by Serial by Group F(8.51,544.47)=0.66, p=.733
6	F(1,45)=2.92, p=.094	1. Length by Group F(2.54,114.21) =0.44, p=..694 2. Serial by Group F(2.08,93.76) = 1.15, p=.323	1. Length by Serial by Group F(8.24,370.81)=1.30, p=.241 **2. Length (span+2 vs span+4&+6) by Serial (pos 5 vs pos4&3&2&1) by Group F(1,45)=5.08, p=.029** **3. Length (span+4 vs span+6) by Serial (pos 2 vs pos1) by Group F(1,45)=7.06, p=.011** 4. Length (span+4 vs span+6) by Serial (pos 4 vs pos3&2&1) by Group F(1,45)=3.08, p=.086

Only orthogonal contrasts describing interactions that were statistically significant or which approached significance are included.

Table 6: Correlations (Spearman's rho) between the Updating Measures and Indices of Drug Use.

	Ecstasy	Cannabis	Cocaine
Frequency of Use[1]			
Letter updating	-.161	-.044	-.025
Spatial Updating	-.168*	-.037	-.042
Amount Used During Previous 10 Days[1]			
Letter updating	-.035	-.053	-.012
Spatial Updating	-.232**	-.009	-.105
Total Lifetime Use[1]			
Letter updating	-.178*	-.031	-.059
Spatial Updating	-.180*	-.015	-.033
Average Weekly Dose[1]			
Letter updating	-.211*	-.025	-.048
Spatial Updating	-.191*	-.009	-.003
Weeks Since Last Use			
Letter updating	.023	.127	-.054
Spatial Updating	.001	.084	.134

1. Nonusers are coded as zero.

** p<.01; * p<.05

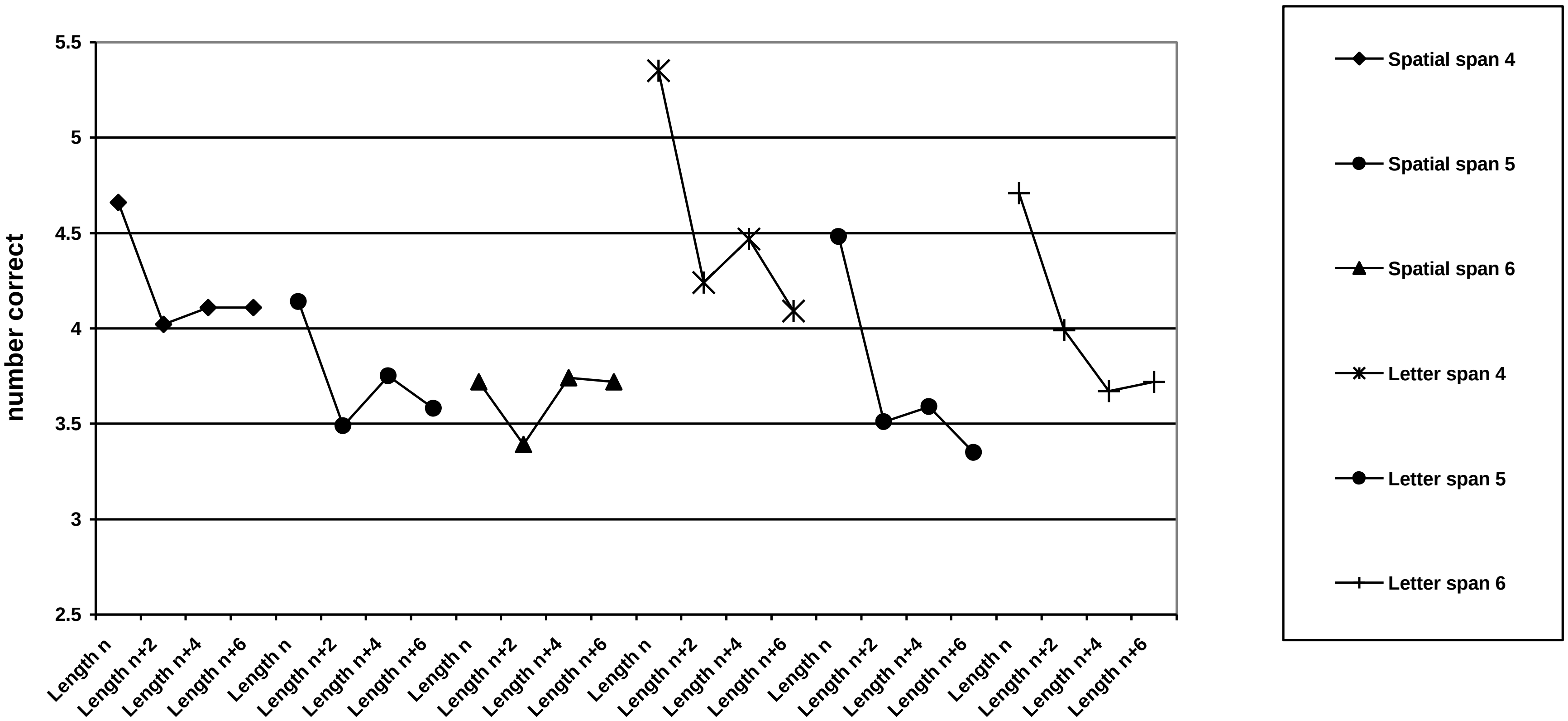


Figure 1. Number of Spatial Locations and Letters Recalled for Participants with Different Spans and for Sequences of Different Length

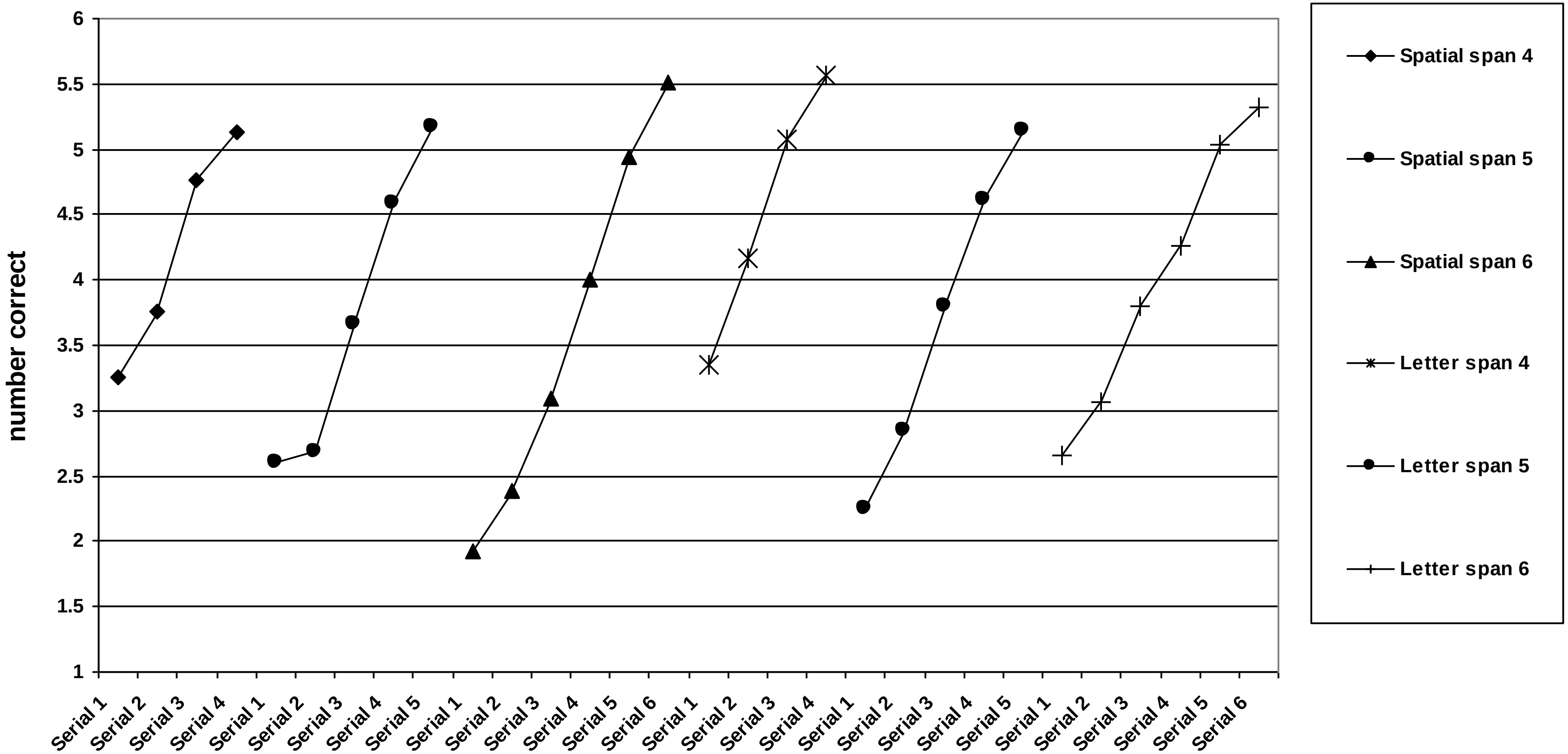


Figure 2. Number of Spatial Locations and Letters Recalled for Participants with Different Spans and for Different Serial Positions

Figure 3. Spatial Updating Span 4 Participants' Length (6 versus 8 and 10) by Serial Position (1 to 3 versus 4) by Group Interaction

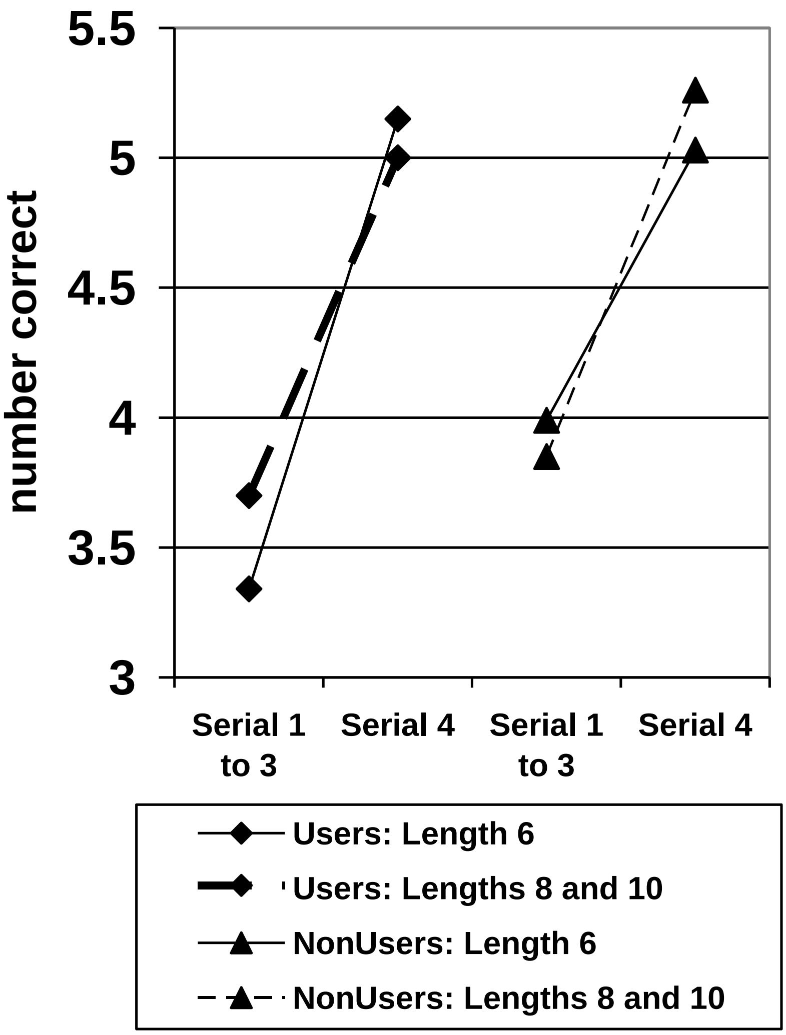


Figure 4. Spatial Updating Span 4 Participants' Length (8 versus 10) by Serial Position (1 to 2 versus 3) by Group Interaction

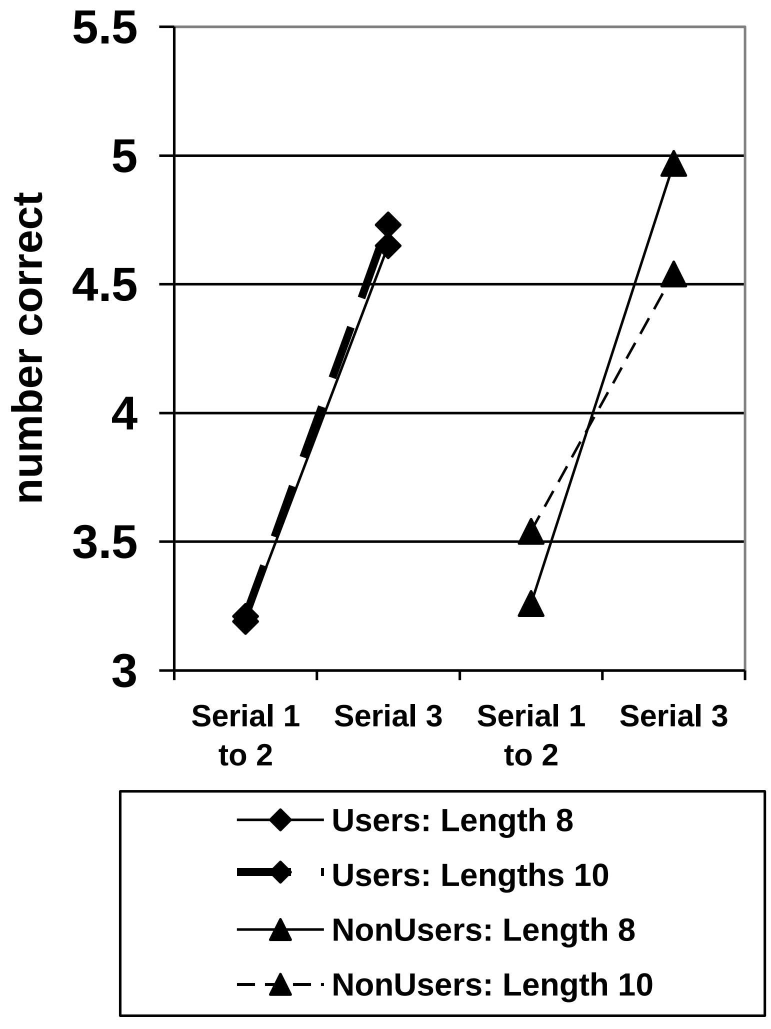


Figure 5: Spatial Updating Span 5 Participants' Length (5 versus 7 to 11) by Serial Position (1 to 4 versus 5) by Group Interaction

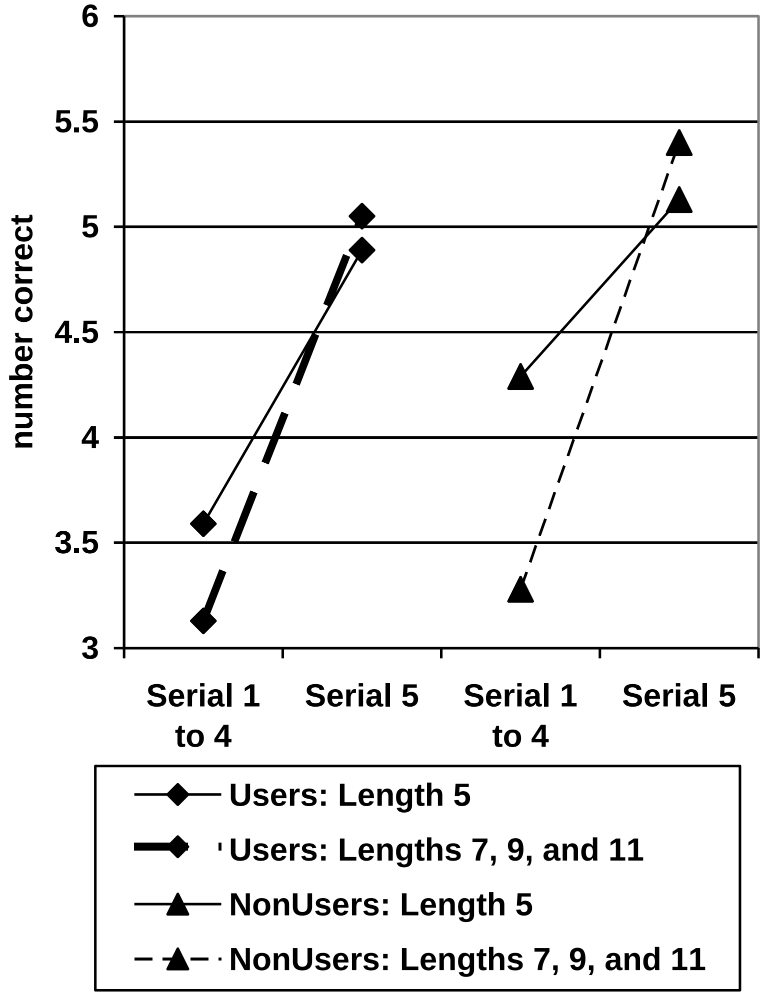


Figure 6: Letter Updating Span 6 Participants' Length (8 versus 10&12) by Serial Position(1 to 4 versus 5) by Group Interaction

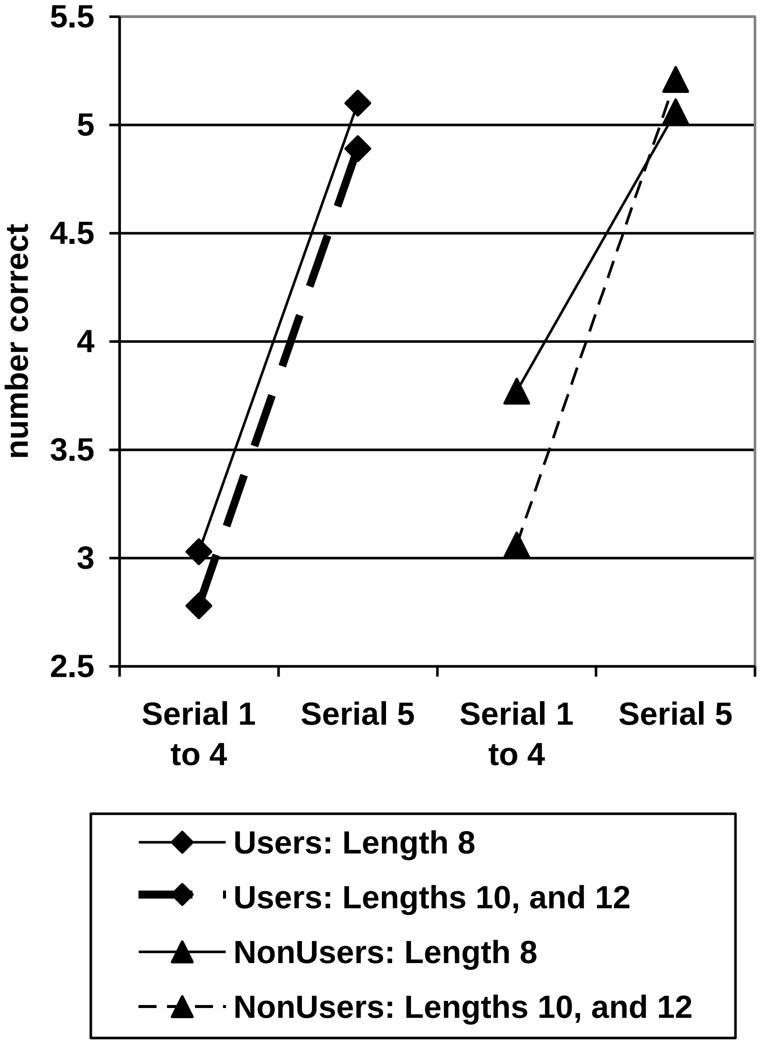
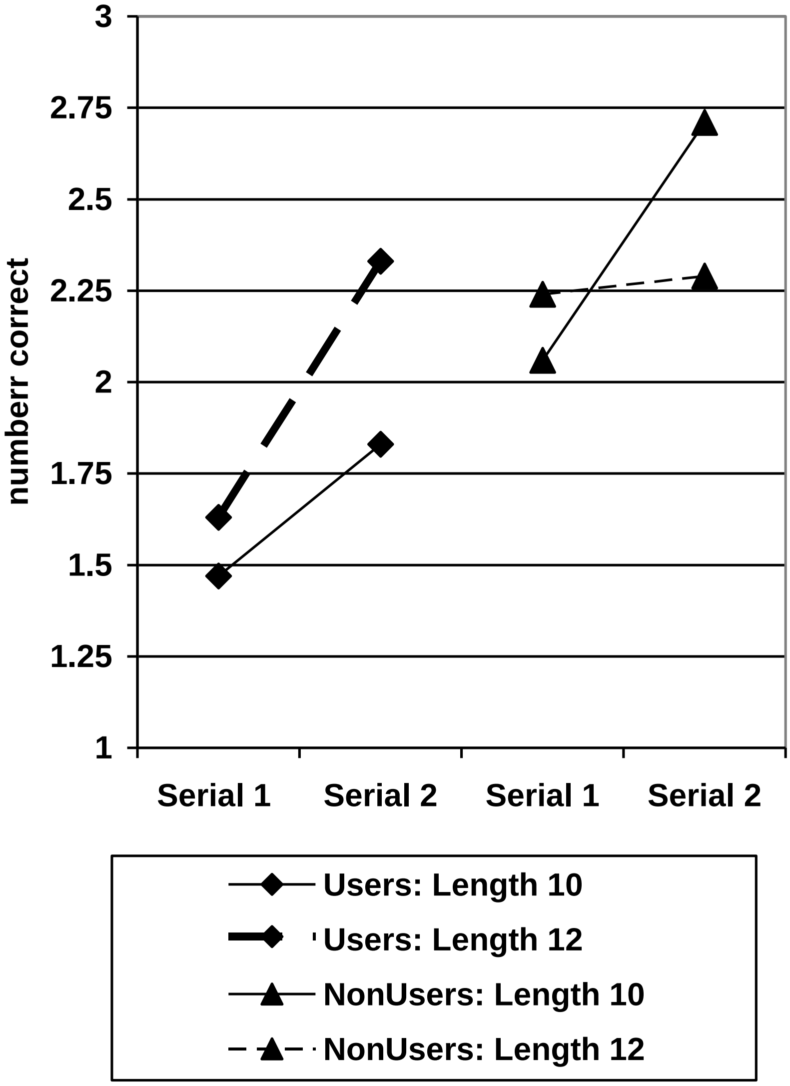


Figure 7:
Letter Updating Span 6 Participants' Length (10 versus 12) by Serial Position(1 versus 2) by Group Interaction



[1] These trends were associated with statistically significant main effects of serial position. For spatial updating, $F(1.81,106.54)=139.70$; $F(3.23,158.19)=247.86$; and $F(3.38,74.36)=124.04$; for span 4, 5, and 6 respectively, and for letter updating, $F(1.93,57.95)=78.09$; $F(2.65,169.56)=272.49$; and $F(2.08,93.76)=106.52$; for span 4, 5, and 6 respectively, $p<.001$ in all six cases. Where Mauchley's test of sphericity was statistically significant, Greenhouse-Geisser epsilon adjusted degrees of freedom are reported.

[2]With respect to spatial updating these trends were associated with statistically significant main effects of sequence length, $F(3,177)=10.66$; $F(3,147)=8.51$; for span 4, and 5 respectively, $p<.001$ in both cases. For letter updating the predicted statistically significant main effect of sequence length was present in all three analyses: $F(3,90)=19.81$; $F(3,192)=34.17$; and $F(2.54,114.21)=18.98$ for span 4, 5, and 6 respectively, $p<.001$ in all cases. Where Mauchley's test of sphericity was statistically significant, Greenhouse-Geisser epsilon adjusted degrees of freedom are reported.

[3] Four users, and six nonusers had simple spatial spans equal to three. These individuals were excluded from Table 4 and from the spatial updating analyses reported in Table 5.

[4] The updating scores were aggregated by working out average recall for each serial position, performance across serial positions was then averaged so as to produce a single score for each sequence length. These were then further averaged to produce a single (comparable) composite score for each participant.

[5] The correlations between cigarettes smoked per day and letter and spatial updating were respectively: -.039 and -.088; and between units of alcohol consumed per week and letter and spatial updating .038 and .000 respectively; $p>.05$ in all cases.